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(54) **Phenethylamine derivatives and intermediates therefor.**

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J. ORGANIC CHEMISTRY, vol. 33, no. 11, November 1968, pages 4275-4278, Washington, D.C., US; E.M. KAISER et al.: "Synthesis of bêta-hydroxyamides from phenylacetamides and ketones or aldehydes by means of alkali amides and N-butyllithium"

The file contains technical information submitted after the application was filed and not included in this specification

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CHEMICAL ABSTRACTS, vol. 96, no. 7, 15th February 1982, page 583, no. 51895k, Columbus, Ohio, US; S. MUTAK et al.: "Synthesis and pharmacological activity of 2-aryl-2-(1-cyclohexenyl)-butylamine derivatives"

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CHEMICAL ABSTRACTS, vol. 95, no. 3, 20th July 1981, page 637, no. 24410w, Columbus, Ohio, US; S. MUTAK et al.: "Synthesis and pharmacological activity of some 2-alkyl-2-cycloalkyl-2-phenylethylamines"

COLLECTION CZECHOSLOV. CHEM. COMM., vol. 28, 1963, pages 1031-1043, Prague, CZ; M. RAJSNER et al.: "Synthetische Analgetika IV. N-substituierte Piperidine und 4-Phenyl-1,2,3,6-Tetrahydropyridine"

Description

The present invention relates to novel phenethylamine derivatives useful as pharmaceuticals and to novel amines, amides and nitriles useful as intermediates.

FR 6408M discloses a class of β-hydroxynitriles having the formula Ia

$$HO—CR_4R_5—CR_1R_2—C\equiv N \qquad (Ia)$$

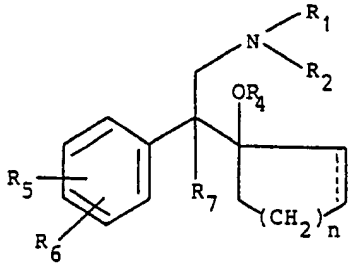
where R_1 is hydrogen or lower alkyl, R_2 is lower alkyl (other than methyl when R_1 is hydrogen) or phenyl and $HO—CR_4R_5$ is C_5—C_7 1-hydroxycycloalkyl and their reduction to form amines having the formula Ib

$$HO—CR_4R_5—CR_1R_2—CH_2NH_2 \qquad (Ib)$$

by hydrogenation. Roux-Schmitt et al., Synthetic Communications 11(2), 85—94 (1981) discloses α-(1-hydroxy-2-cyclohexen-1-yl)-4-methoxybenzeneacetonitrile and α-(1-hydroxy-2-cyclohexen-1-yl)benzeneacetonitrile. The present invention includes novel intermediate compounds differing from those of formulae Ia and Ib in that R_2 is replaced by phenyl which is substituted.

Kaiser et al., J. Org. Chem. *33*, 4275—4278 (1968) discloses α-(1-hydroxycyclohexyl)benzeneacetamide, α-(1-hydroxycyclohexyl)-N-(methyl)benzeneacetamide and α-(1-hydroxycyclopentyl)benzeneacetamide. The present invention includes novel intermediates differing from these three amides in that the benzene ring is substituted.

In accordance with this invention there is provided a group of phenethylamine derivatives which are central nervous system antidepressants. The end compounds of this invention present the following structural formula



(I)

where the dotted line represents optional unsaturation;

R_1 is hydrogen or alkyl of 1 to 6 carbon atoms;

R_2 is alkyl of 1 to 6 carbon atoms;

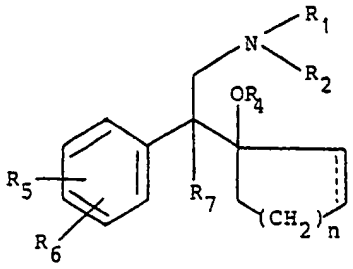
R_4 is hydrogen, alkyl of 1 to 6 carbon atoms, formyl, or alkanoyl of 2 to 7 carbon atoms;

R_5 and R_6 are independently hydrogen, hydroxyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, cyano, nitro, alkylmercapto of 1 to 6 carbon atoms, amino, alkylamino of 1 to 6 carbon atoms, dialkylamino in which each alkyl group is of 1 to 6 carbon atoms, alkanamido of 2 to 7 carbon atoms, halo, trifluoromethyl, or, when taken together, methylene dioxy;

R_7 is hydrogen or alkyl of 1 to 6 carbon atoms; and n is one of the integers 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt thereof.

The preferred compounds are those of the formula



(I)

in which the dotted line and R_4 are defined *supra*;

R_1 is hydrogen or alkyl of 1 to 3 carbon atoms;

R_2 is alkyl of 1 to 3 carbon atoms;

R_5 is hydrogen, hydroxy, alkoxy of 1 to 3 carbon atoms; chloro, bromo, trifluoromethyl or alkyl of 1 to 3 carbon atoms;

R_6 is alkyl of 1 to 3 carbon atoms, alkoxy of 1 to 3 carbon atoms, chloro, bromo, trifluoromethyl or alkanoyloxy of 2 to 3 carbon atoms;

R_7 is hydrogen or alkyl of 1 to 3 carbon atoms;

or a pharmaceutically acceptable salt thereof.

The most preferred compounds are those in which R_5 and R_6 are in meta or para positions and n is 2.

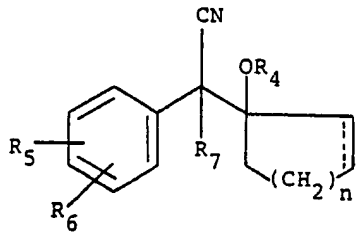
As subgeneric aspects of the end compounds of the invention there are included the compounds where (a) R_7 is hydrogen, the dotted line represents saturation and neither R_5 nor R_6 is alkanamido of 2 to 7 carbon atoms and (b) R_2 is $—CH_2—R_8$ where R_8 is alkyl of 1 to 5 carbon atoms, neither R_5 nor R_6 is cyano, nitro, alkylmercapto of 1 to 6 carbon atoms, amino, alkylamino of 1 to 6 carbon atoms, dialkylamino in which each alkyl group is of 1 to 6 carbon atoms or alkanamido of 2 to 7 carbon atoms and A and R_7 are as defined under (a) except that R_4 is hydrogen or alkanoyl of 2 to 7 carbon atoms and n is 1, 2, 3 or 4.

The compounds in which R_4 is formyl or alkanoyl of 2 to 7 carbon atoms are not nearly as patent as the corresponding free hydroxy bearing derivatives in the test procedures employed and disclosed herein. However, in long term therapy the acyloxy derivatives will act as pro drugs as the acyl group is removed *in vivo* either via acid hydrolysis in the stomach or enzymatically.

The pharmaceutically acceptable acid addition salts of the basic compounds of this invention are formed conventionally by reaction of the free base with an equivalent amount of any acid which forms a non-toxic salt. Illustrative acids are either inorganic or organic, including hydrochloric, hydrobromic, fumaric, maleic, succinic, sulfuric, phosphoric, tartaric, acetic, citric, oxalic and similar acids. For parenteral administration, the use of water soluble salts is preferred, although either the free base of the pharmaceutically acceptable salts are applicable for oral or parenteral administration of the antidepressant agents of this invention. The halo substituent representing R_5 or R_6 is intended to include the chloro, bromo, iodo or fluoro substituents.

The compounds of this invention are produced by reaction of a cycloalkanone or a cyloalkenone with an appropriately substituted (ortho or para) phenylacetonitrile anion following the procedure of Sauvetre et al., Tetrahedron, *34*, 2135 (1978) followed by reduction (catalytic hydrogenation, borane reducing agents, $LiAlH_4$, etc.) of the nitrile to a primary amine and alkylation of the amine. In the presence of cyclo aliphatic unsaturation, lithium aluminium hydride is the preferred reducing agent. Subsequent acylation of the α-cycloaliphatic hydroxyl group and any phenolic hydroxyl group present may be effected conventionally with a formylating agent such as formyl fluoride or an alkanoic acid halide or anhydride. Symmetrical N-methylation may be accomplished via a modified Eschweiler-Clarke procedure employing a large excess of water as illustrated by Tilford et al., J.A.C.S. *76*, 2431 (1954); alternatively the procedure of Borch and Hassid, J. Org. Chem., *37*, 1653 (1972) using sodium cyanoborohydride and formaldehyde may be employed. Non symmetrical N-alkylation or monoalkylation may be accomplished by stepwise alkylation of the N-trifluoroacetate as illustrated by R. A. W. Johnstone et al., J. Chem. Soc., (C) 2223 (1969). Where R_4 is alkyl it is introduced prior to reduction of the nitrile by conventional O-alkylation.

Intermediate nitriles pepared during the production of the antidepressant agents of this invention may be depicted by the structural formula



(IV)

in which the dotted line represents optional unsaturation, and

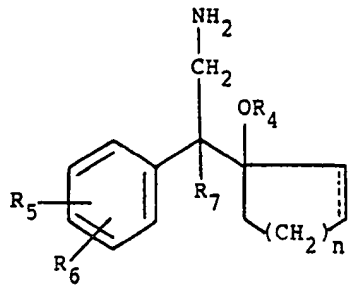
R_4 is hydrogen or alkyl of 1 to 6 carbon atoms;

R_5 and R_6 are ortho or para substituents, independently selected from the group consisting of hydrogen, hydroxyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, aralkoxy of 7 to 9 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, alkylmercapto of 1 to 6 carbon atoms, halo or trifluoromethyl;

R_7 is hydrogen or alkyl of 1 to 6 carbon atoms; and n is one of the integers 0, 1, 2, 3 or 4.

Such nitriles are new and represent an aspect of the invention subject to the provisos that the dotted line represents saturation and that R_5 and R_6 are not both hydrogen.

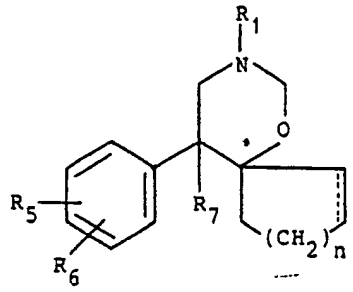
The primary amines used as intermediates for preparing end products of the invention may be prepared from the nitrile or by reduction of an N-unsubstituted amide. Primary amines that may be prepared comprehend the compounds of formula VI



(VI)

where the dotted line, R_4, R_5, R_6, R_7 and n are as defined below under formula X. Such compounds are new and represent an aspect of the invention subject to the proviso that R_5 and R_6 are not both hydrogen. The primary amines may be in the form of pharmaceutically acceptable salts.

Symmetrical N,N-dimethylation may be performed readily by reaction of the primary amono derivative with formaldehyde, formic acid in a large excess of water. An intermediate, 3-aza-1-oxaspiro[5.5]undecane is formed during the reaction and is isolated. It presents the following structural formula



(V)

in which the dotted line represents optional unsaturation,

R_1 is methyl;

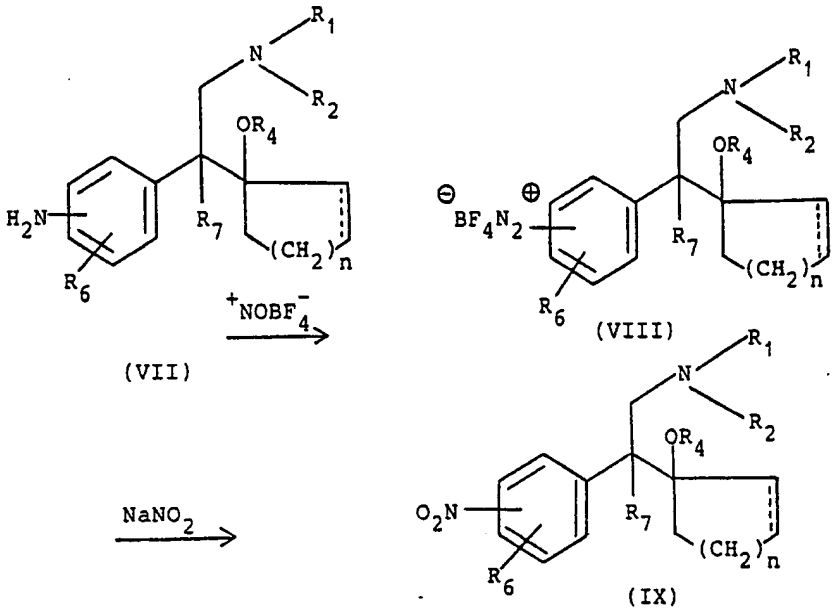
R_5 and R_6 are ortho or para substituents independently selected from the group consisting of hydrogen, hydroxyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, aralkoxy of 7 to 9 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, alkylmercapto of 1 to 6 carbon atoms, halo or trifluoromethyl;

R_7 is hydrogen or alkyl of 1 to 6 carbon atoms; and n is one of the integers 0, 1, 2, 3 or 4.

These oxaspiro[5.5]undecane intermediates possess similar activity to the corresponding open-ring tertiary amino end compounds of the invention. For example, the oxazine produced in Example 3 is hereinafter compared, in its properties, with the corresponding dimethylamino end compound of Example 3. The end compound is produced from the corresponding oxazine by prolonged reflux in the presence of aqueous formic acid.

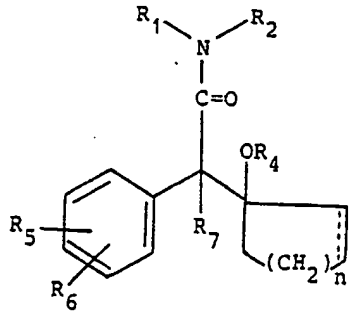
An alternative, and preferred, mode of preparing the compounds of this invention involves the reaction of a cycloalkanone or cycloalkenone with an appropriately substituted phenylacetamide anion following the procedure of Sauvetre et al., ibid., followed by a reduction of the amide with lithium aluminium hydride or a borane reducing agent, except in the case of cycloaliphatic unsaturation as discussed, *supra*, to the corresponding amine. This process is preferred because it is considerably more facile when dealing with meta-substituents or halo-substituted phenylacetamide reactants which pose some problems when proceeding through the acetonitrile intermediate. This route to the desired end products also permits one to readily vary the values R_1 and R_2 in the initial reactant.

The cyano substituent representing R_5 and/or R_6 is introduced after all reduction steps have been completed by displacement of an R_5—R_6 halo substitution with cuprous cyanide. The amino substituents representing R_5 and/or R_6 are protected throughout the reaction sequence with a protecting group such as 1,1,4,4-tetramethyl-1,4-dichlorosilylethylene which completely blocks the amino nitrogen atom from undesireable reactions. After completion of the reaction sequence, the amino group is deprotected and alkylated or acylated by conventional means to provide a mono- or di-alkylamine or an alkanamido group in each case of 1 to 6 carbon atoms. The nitro substituent representing R_5 and/or R_6 is introduced and an aromatic substituent by diazotization of the aromatic amine followed by treatment with alkaki metal nitrite in the presence of copper or by formation of the diazonium tetrafluoroborate and reaction with an alkali metal nitrite, thusly:



The cyano substituent may be introduced via the diazonium salt with cuprous cyanide in analogous manner.

The amide that may be prepared as intermediate for the preparation of an end compound of this invention may be depicted by the following structural formula



(X)

in which the dotted line represents optional unsaturation,

R_1 is hydrogen or alkyl of 1 to 6 carbon atoms;

R_2 is hydrogen or alkyl of 1 to 6 carbon atoms;

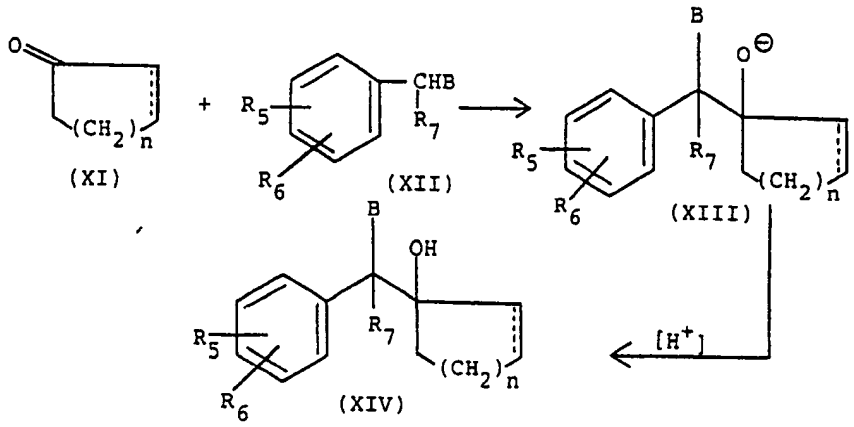
R_4 is hydrogen or alkyl of 1 to 6 carbon atoms;

R_5 and R_6 are, independently, hydrogen, hydroxyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, aralkoxy of 7 to 9 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, alkylmercapto of 1 to 6 carbon atoms, N-protected amino, halo, trifluoromethyl, or when taken together, methylenedioxy;

R_7 is hydrogen or alkyl of 1 to 6 carbon atoms; and n is one of the integers 0, 1, 2, 3 or 4.

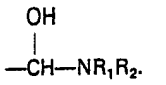
Such amides are new and represent an aspect of the invention subject to the proviso that R_5 and R_6 are not both hydrogen. When R_4 is alkyl it is introduced prior to reduction. The protecting group employed to prevent reaction at the amino substituent representing R_5 and/or R_6 is any protecting group that will completely prevent reaction at a primary —NH_2 substituent, such as 1,2-[bis-dimethylsilylchloride]ethane.

More indirect routes for synthesis of the antidepressant compounds of this invention involve the reaction of a cycloalkanone or a cycloalkenone with an anion of an appropriately substituted phenylacetic acid, salt, ester, aldehyde or alcohol



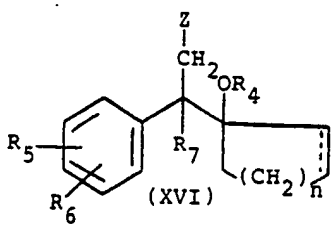
where B represents a carboxyl group or its salts or ester or a —CHO or CH_2OH functional group.

The carboxylic acid group may be converted to an acid halide, active ester or anhydride and directly reacted with the desired amine to yield, after reduction of the resulting amide, the end products of this invention. Also, the carboxylic acid group may be reduced with diisobutyl aluminum hydride or lithium aluminum hydride to obtain the corresponding aldehyde. The ester is readily converted to the aldehyde with diisobutyl aluminum hydride or to the alcohol with lithium aluminum hydride. The aldehyde may be condensed with hydroxylamine to afford the oxime —CH=NOH; with ammonium or a primary amine to afford an imine $—CH=NR_1$ or with a primary or secondary amine to afford

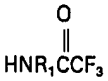


The alcohol $—CH_2OH$ may be converted to the corresponding nitro derivative by producing an organic sulfonate (mesyl ester) or halide followed by displacement with an inorganic nitrite. Reduction of these intermediates yields the primary amine intermediates or the secondary or tertiary amine end products of this invention. The alcohols may be converted to mesylates or tosylates, reacted with KCN to afford the nitrile, converted to the amide and subjected to a Hoffman rearrangement with bromine or chlorine and an alkali metal hydroxide.

Additional routes to the desired products include the reaction of ammonia or HNR_1R_2 with

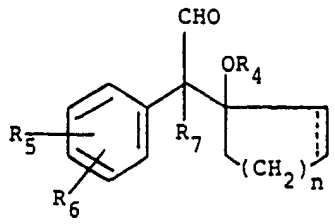


where Z is a leaving group such as a halogen or an organo sulfonyloxy (mesyl, tosyl and the like) group under conventional conditions. If desired, the amine reactant may be initially blocked with a relatively labile acyl group such as trifluoroacetyl to provide a reactant of the formula



prior to reaction with the alkylating reactant employing KOH and a very polar solvent such as dimethylsulfoxide, to provide a tertiary amide from which the acyl group may be readily removed to prepare the compound for non-symmetrical N-alkylation to insert R_2. Rather than N-alkylate, one may acylate or react the secondary amine with an aldehyde and subsequently reduce the amide or Schiff base. Similarly, reaction of the amine with an alkylchloroformate affords, upon reduction, an N-methylated amine. $LiAlH_4$ is a good reducing agent for these processes.

Reductive amination of the aldehyde



(XVIII)

with ammonia, a primary amine or a secondary amine (Leuckart reaction) also yields the desired end products.

The compounds of formula I where A has formula III or a salt thereof can be prepared by dehydration of a corresponding compound where A is of formula II where R_4 is hydrogen.

During the course of the synthesis of the end compounds of the invention by means of processes identified above, any hydroxy group represented by $-OR_4$, R_5 or R_6 may be in the free form or in the form of hydroxy protected by a removable protecting group, except of course, that the hydroxy group is not protected in any case where it is intended to participate in a reaction. The protected form is recommended where the hydroxy group may otherwise undergo an undesired reaction. Examples of protecting groups for hydroxy are given in Proctive Groups in Organic Chemistry edited by J. F. W. McOmie, Chapters 3 and 4 (pages 95—182), published by Plenum Press (1973), and Protective Groups in Organic Chemistry by T. W. Greene, Chapters 2 and 3 (pages 10 to 113) published by John Wiley and Sons (1981). The protecting group may be removed at a suitable later stage in the synthesis. Similarly any amino or alkylamino group may be in a protected form where appropriate during the course of the synthesis of the end compounds. Protecting groups for amino are described in Chapter 2 (pages 43 to 94) of the McOmie book and Chapter 7 (pages 218 to 286) of the Greene book.

The end products contain either one or two asymmetric centers depending upon the saturated and unsaturated state of the cycloaliphatic ring, respectively. Individual stereoisomeric forms may be obtained or separated by standard procedures. For instance separation of the mixture in the case of an amine or carboxylic acid may be carried out by neutralisation with a suitable optically active compound to form salts which can be separated. Example 33 illustrates the typical resolution of the product of Example 3, Compound A.

The antidepressant activity of the end compounds of this invention was established by demonstrating that they (1) inhibit ^{3}H-imipramine binding in brain tissue when tested by a method analogous to that of Raisman et. al., Eur. J. Pharmacol. *61*, 373—380 (1980); (2) inhibit synaptosomal uptake of norepinephrine (^{3}H—NE) and serotonin (^{14}C—5—HT) following the test procedure of Wood et. al., J. Neurochem. *37*, 795—797 (1981); and antagonize reserpine induced hypothermia when tested in accordance with the procedure of Askew, Life Sci. *1*, 725—730 (1963).

The results of the these procedures affirmed the anti-depressant activity of the end compounds of this invention in agreement with the most widely acceptable theory of antidepressant activity and in correlation of activity with known tricyclic antidepressants. In at least two instances, namely, with the dimethylamino product of Example 3, and 4-chloro product in Example 11, the undesirable attribute of classical antidepressants observed as an anticholinergic property which is reflected by the inhibition of binding of the muscarinic receptor ligand, 3H-quinuclidinyl benzilate (QNB), and in the inhibition of carbachlol-stimulated contraction of the guinea-pig ileum, is missing. Also missing is the attribute of classical antidepressants observed as an antihistaminic property which is reflected by the inhibition of the H_1 histamine receptor ligand, 3H-pyrilamine, and in the inhibition of histamine-stimulated contraction of the guinea-pig ileum.

As representative examples of the activity profile of the end compounds of this invention, the following data for testing of the dimethylamino product of Example 3, hereinafter Compound A, its oxazine variant, hereinafter Compound B, the 4-chloro product of Example 11, hereinafter referred to as Compound C, the 4-bromo product of Example 15, hereinafter referred to as Compound D, the 3-chloro product of Example 17, hereinafter referred to as Compound E, the 3-bromo product of Example 16, hereinafter referred to as Compound F, and the 3,4-dichloro product of Example 19, hereinafter referred to as Compound G, are presented as follows:

Inhibition of ^{3}H-imipramine binding: Compound A (HCl Salt) exhibited an inhibition constant (K_i) vs. ^{3}H-imipramine of 90nM, making it a fairly potent ligand at this receptor site. Compound B was somewhat less potent, with a K_i of 350nM. Compound C was virtually equipotent with Compound A, exhibiting a K_i vs. ^{3}H-imipramine of 100 nM. While not as potent as imipramine (K_i=1.7nM), these values fall in the range of desmethylimipramine (DMI) (K_i=130nM) and other tricyclic antidepressants. Atypical antidepressants (non-tricyclic which have been tested, exhibit K_i's greater than 5000nM in this assay. Compounds D, E, F and G exhibited inhibition constants of 62, 130, 52 and 37, respectively. Compounds A through G, representative of the other compounds of this invention, are thus comparable to known tricyclic antidepressants in this test.

Inhibition of synaptosomal NE and 5—HT uptake:
Results of the inhibition of NE and 5—HT synaptosomal uptake, expressed as the inhibitory concentration at which the rate of uptake was reduced to 50 percent (IC_{50}), are presented in the table below, where they are compared with the values for imipramine, DMI and amitriptyline:

Compound	IC_{50} (μM) NE	5—HT
Imipramine	0.26	0.12
DMI	0.15	3.0
Amitriptyline	0.50	0.60
Compound A	0.64	0.21
Compound B	4.7	2.9
Compound C	0.33	0.25
Compound D	0.21	0.11
Compound E	0.16	0.32
Compound F	0.11	0.23
Compound G	0.07	0.08

These results show that Compounds A and C to G are approximately equipotent to imipramine in NE and 5—HT uptake inhibition. Again, Compound B is somewhat less potent.

Inhibition of ^3H—QNB binding: In the QNB receptor binding assay, the Compounds A and C—G exhibited an IC_{50} greater than 10^{-5} molar and were therefore essentially inactive. Imipramine and DMI exhibit K_i's of 37 nM and 50 nM, respectively. These results suggest that, unlike the tricyclic antidepressants, Compounds A and C—G would have no muscarinic anticholinergic actions.

Inhibition of Carbachol-stimulated contraction of guinea-pig ileum: While imipramine at 1 μM exhibis a K_B of approximately 100 nM against carbachol-stimulated contraction of the guinea-pig ileum, Compound A was inactive at 1 μM. This result supports the suggestion of a lack of muscarinic anticholinergic action of Compound A.

Inhibition of ^3H-pyrilamine binding: While DMI exhibits a K_i versus ^3H-pyrilamine binding of 124 nM, Compound A was inactive. Compounds D—G exhibited an IC_{50} greater than 10^{-5} molar. These results suggest that, unlike tricyclic antidepressants, Compounds A and D—G have no antihistaminic property.

Inhibition of histamine-stimulated contraction of the guinea-pig ileum: Imipramine at 1 μM inhibits the histamine- stimulated contraction of the guinea-pig ileum with an aporoximate K_B of 8 nM. Compound A, in contrast, has no effect in this test at a concentration of 1 μM. This result supports the notion that Compound A has no antihistaminic action.

Antagonism of reserpine-induced hypothermia: The minimum effective dose (M.E.D.) of compounds A through G established in antagonism of reserpine-induced hypothermia in mice (n = 8 per group) in relation to desmethylimipramine (DMI) were:

Compound	Dose, mg/kg, i.p.
DMI	0.4
A	10.0 (and p.o.)
B	30.0
C	10.0
D	3.0
E	1.0
F	1.0
G	3.0

All mice received 5 mg/kg reserpine s.c. 18 h prior to test compound.

DMI, and Compounds A to G, are of approximately equal efficacy in the reversal of reserpine-induced hypothermia. Compound B was less potent than Compound A, Compound C was approximately equipotent with Compound A, Compounds D and G were approximately three times as potent as Compound A, and Compounds E and F were approximately ten times as potent as Compound A in the study.

Hence, the end compounds of this invention are useful in the treatment of depression, for which purpose they may be administered orally or parenterally in an amount sufficient to alleviate the symptoms of depression. The actual amount of antidepressant agent to be used will vary with the severity and nature of the depressed state, the animal being treated and the level of relief sought. In the human, an oral dose of from about 2 to about 50 milligrams, administered as needed represents appropriate posology. Intramuscular administration of from about 1 to 25 milligrams provides a dosage comparable to that specified for oral administration. As with other antidepressants, therapy should be initiated with lower dosages and increased until the desired symptomatic relief is obtained.

Pharmaceutical compositions containing the antidepressant compounds of this invention represent an additional aspect of this invention. The active ingredient can be compounded into any of the usual oral dosage forms including tablets, capsules and liquid preparations such as elixirs and suspensions containing various colouring, flavouring, stabilizing and flavour masking substances. For compounding oral dosage forms, the active ingredient can be mixed with various conventional tabletting materials such as starch, calcium carbonate, lactose, sucrose and dicalcium phosphate to aid the tabletting or capsulating process. Magnesium stearate, as an additive provides a useful lubricant function when desired.

The active ingredients can be dissolved or suspended in a pharmaceutically acceptable sterile liquid carrier, such as sterile water, sterile organic solvent or a mixture of both. Preferably a liquid carrier is one suitable for parenteral injection. Where the active ingredient is sufficently soluble it can be dissolved in normal saline as a carrier; if it is too insoluble for this it can often be dissolved in a suitable organic solvent, for instance aqueous propylene glycol or polyethylene glycol solutions. Aqueous propylene glycol containing from 10 to 75% of the glycol by weight is generally suitable. In other instances other compositions can be made by dispersing the finely divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution, or in a suitable oil, for instance arachis oil. Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilised by intramuscular, intraperitoneal or subcutaneous injection.

Preferably the pharmaceutical compositions is in unit dosage form, e.g. as tablets or capsules. In such form, the composition is sub-divided in unit doses containing appropriate quantities of the active ingredient; the unit dosgae forms can be packaged compositions, for example, packeted powder or vials or ampoules. The unit dosage form can be a capsule, cachet or tablet itself, or it can be the appropriate number of any of these in package form. The quantity of the active ingredient in a unit dose of composition may be varied or adjusted from 2 mg. or less to 50 mg. or more, according to the particular need and the activity of the active ingredient.

The following examples illustrate the preparative technique employed in production of the compounds of the invention.

Example 1

1-[Cyano(p-methoxyphenyl)methyl]cyclohexanol

p-Methoxyphenylacetonitrile (50 gm, 0.3 mole) was added to dry tetrahydrofuran (250 ml) and the solution cooled to −70°C. under nitrogen. n-Butyl lithium in hexane (210 ml, 0.3 mole) was added dropwise.

with stirring. The temperature was maintained below −50°C. and a yellow precipitate appeared. After the addition was complete, the reaction mixture was maintained below −50°C. for 30 minutes and cyclohexanone (35 ml, 0.3 mole) was added. After a further 45 minutes below −50°C, the temperature was allowed to rise to 0°C. and a saturated ammonium chloride solution was added. The layers were separated and the aqueous layer extracted with diethyl ether. The combined organic solution was washed with brine, dried over magnesium sulphate and evaporated. The product crystallized (25.2 gm, m.p. 125—127°C.).

Mass Spectral Analysis: Molecular weight 245 [$(M + 1)^+$ by C.I.M.S.].

N.M.R. Analysis: δ 7.32, 6.95; (4H quartet, p-substituted aromatic) 3.8 (3H singlet, O—CH_3); 3.76 (1H, singlet, CH—CN); 1.56 (10H, multiplet, aliphatic cyclohexyl) ppm.

Example 2

1-[2-amino-1-(p-methoxyphenyl)ethyl]cyclohexanol

1-[cyano(p-methoxyphenyl)methyl]cyclohexanol (12 g, 0.05 mole) was dissolved on warming in a mixture of ammonia-ethanol (20% v/v, 250 ml) and hydrogenated in a Parr apparatus over 5% rhodium on alumina (2.8 gm). The catalyst was filtered, washed well with ethanol and the combined filtrate evaporated and dried under vacuum yielding an oil (12 gm).

Mass Spectral Analysis: Molecular weight 249 $(M + 1)^+$ by C.I.M.S.

Thin Layer Chromatography: single spot, ninhydrin positive [chloroform-methanol-acetic acid (80:10:10 v/v)].

Example 3

5-(4-methoxyphenyl)-3-methyl-3-aza-1-oxaspiro(5.5)-undecane and 1-[2-dimethyl-amino)-1-(4-methoxyphenyl)ethyl]cyclohexanol

1-[2-amino-1-[p-methoxyphenyl)ethyl]cyclohexanol (12 gm; 0.048 mole) was treated wth a mixture of formaldehyde (11 ml), formic acid (14.5 ml, 88%) and water (125 ml) and heated at 100°C. for five hours. The reaction mixture was cooled and extracted with ethyl acetate. This extract was discarded. The aqueous residue was cooled in ice, rendered basic by the addition of solid potassium hydroxide, saturated with sodium chloride and thrice extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous potassium carbonate and evaporated to an oily residue (8 gm). This mixture of products was chromatographed on 1 kg of Mallinckrodt Silicar CC7 silica gel and the progress of the chromatography was monitored by thin layer chromatography using a system comprising ethanol: 2N ammonia:ethyl acetate:cyclohexane 45:8:100:100 (v/v). Fractions containing the desired products were combined and the hydrochloride salts prepared using 4-N-isopropanolic HCl. The yields of the free bases were 1.4 gm (spiro compound) and 4.6 gm (dimethyl- amine) respectively.

Compound B

5-(4-methoxyphenyl)-3-methyl-3-aza-1-oxaspiro(5.5)undecane

Melting Point: 242—244°C.

Mass Spectral Analysis: Molecular weight 275 $(M + 1)^+$ by C.I.M.S.

N.M.R. Analysis: δ 7.22, 6.96 (4H quartet, p-substituted aromatic) 4.78 (2H quartet, O—CH_2—NCH_3) 3.8 (4*H*, O—CH_3, CH—CH_2—NCH_3) 3.3 (2H, multiplet CH—CH_2—NCH_3) 2.8 (3*H*. NCH_3) 0.9—1.8 (10H broad multiplet, aliphatic cyclohexyl) ppm.

Compound A

1-[(2-dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol.

The hydrochloride: m.p. 215—217°C.

Mass Spectral Analysis: Molecular weight 279 $(M + 1)^+$ by C.I.M.S. (free base)

N.M.R. Analysis: δ 7.32, 6.98 (4*H* quartet, p-substituted aromatic) 3.78 (3*H*, O—CH_3) 3.64 (2*H*, multiplet $CH_2N(CH_3)_2$) 3.06 (1H, multiplet CH—$CH_2(NCH_3)_2$) 2.74 (6H, $N(CH_3)_2$) 1.38 (10H, broad multiplet, alphatic cyclohexyl) ppm.

Example 4

1-[2-(dimethylamino)-1-(4-methoxyphenyl)-1-(methyl)ethyl]cyclohexanol

14.7 g (0.10 mole) of p-methoxyphenylacetonitrile was dissolved in 250 ml of dry tetrahydrofuran and placed in a dry ice/isopropanol bath under N_2. 69.0 ml of 1.6 M n-butyl lithium (0.11 mole) was added dropwise over 30 minutes and the mixture stirred at −78°C for one hour. The lithium salt of the nitrile precipitated as a yellow solid during this time. 71.0 g (0.50 mole) of methyl iodide was then added and stirring at −78°C continued for an additional hour. The mixture was then poured into saturated ammonium chloride and the product extracted into diethyl ether, washed with saturated sodium chloride and dried over sodium sulfide. It was filtered and evaporated, redissolved in methylene chloride and passed through Florisel®. Evaporation gave 15.0 g of α-(p-methoxyphenyl)propionitrile as an orange oil.

The α-(p-methoxyphenyl)propionitrile prepared above was redissolved in 250 ml of tetrahydrofuran and cooled to −78°C in dry ice/isopropanol. 69.0 ml of 1.6 M n-butyllithium was added over 30 minutes and the mixture stirred for 1 hour under nitrogen. 20 ml of cyclohexanone was then added and stirring at −78°C

was continued for an additional hour. The mixture was poured into saturated ammonium chloride solution and the product extracted with diethyl ether. It was washed with water, saturated sodium chloride and dried over sodium sulfate. Filtration and evaporation gave 21.5 g of white solid. A sample twice recrystallized from benzene had m.p. 129°C and the following analysis:

Analysis for: $C_{16}H_{21}NO_2$
Calculated: C, 74.10; H, 8.16; N, 5.40
Found: C, 73.95; H, 8.04; N, 5.29.

4.0 g (15 mmoles) of the β-hydroxynitrile prepared above was dissolved in 200 ml of tetrahydrofuran and 50 ml of 1M borane tetrahydrofuran complex was added. The mixture was refluxed for 2 hours and allowed to cool. 200 ml of 2N HCl was added and the THF removed *in vacuo*. The aqueous solution was made basic by the addition of solid potassium carbonate and the product extracted with 500 ml of ethyl acetate, washed with saturated sodium chloride and dried over sodium sulphate. This was filtered and evaporated and treated with isopropanolic HCl and diethyl ether to yield 3.3 g of the primary amine, m.p. 209°C.

Analysis for: $C_{16}H_{26}NO_2Cl$
Calculated: C, 64.09; H, 8.74; N, 4.67
Found: C, 63.70; H, 8.60; N, 4.59.

3.0 g (10 mmole) of the primary amine hydrochloride was dissolved in 200 ml of absolute ethanol. 5.0 ml of 37% aqueous formaldehdye and 1.0 g of 10% palladium on carbonate were added and the mixture was treated with 3.4 bars (50 psi) of hydrogen on a Parr shaker for 3 days. The mixture was then filtered and evaporated and the solvent replaced with 300 ml of water and washed with 300 ml of ethyl acetate. The aqueous solution was then made basic with solid sodium carbonate and again extracted with ethyl acetate. The organic extract was washed with saturated brine and dried over sodium sulphate. It was filtered and evaporated and the title compound precipitated as the hydrochloride from isopropanol/ether by the addition of isopropanolic HCl. A second crystallization from isopropanol gave 2.0 g of white solid, m.p. 271°C.

Analysis for: $C_{18}H_{30}NO_2Cl$
Calculated: C, 65.93; H, 9.22; N, 4.27
Found: C, 65.73; H, 8.93; N, 4.20.

Example 5

1-[(α-Aminomethyl)benzyl]-cyclohexanol

Phenylacetonitrile (10 g, 0.08 mole) was added to dry THF (100 ml) and the solution cooled to −70°C. under nitrogen. n-Butyllithium in hexane (64 ml, 0.1 mole) was added dropwise, the temperature being maintained below −40°C. and a yellow precipitate appeared. After addition the reaction mixture was maintained near −70°C for 30 minutes and cyclohexanone (10 g, 0.1 mole) was added. After a further 45 minutes at −70°C. the temperature was allowed to rise to 0°C. and saturated ammonium chloride solution was added. The layers were separated and the aqueous layer extracted with diethyl ether. The combined organic solution was washed with brine, dried over magnesium sulphate and evaporated. The product, 1-[α-cyanobenzyl]-cyclohexanol, crystallized (4.93 g, m.p. 100—102°C).

Mass Spectral Analysis: Molecular weight 215 (M^+).

N.M.R. Analysis: δ 7.4 (5H singlet, aromatic 3.8 (1H, singlet, C*H*— CN) 1.6 (10H, multiplet aliphatic cylohexyl) ppm.

A solution of 1-(α-cyanobenzyl)cyclohexanol (3.43 g, 0.02 mole) in a mixture of methanol and ammonia (9:1 v/v, 60 ml) was hydrogenated in a Parr apparatus over 5% rhodium on alumina (2 g). The catalyst was filtered and the filtrate evaporated. The residue was dissolved in ethyl acetate, washed with brine, dried over magnesium sulfate and evaporated. The hydrochloride m.p. 220—222° (1.2 g) crystallized from diethyl etheracetone.

Analysis for: $C_{14}H_{21}NO{\cdot}HCl$
Calculated: C, 64.29; H, 8.67; N, 5.47%
Found: C, 65.74; H, 8.51; N, 5.56%.

N.M.R. Analysis: (DMSO) δ 7.73 (5H, singlet, aromatic) 3.46 (2H, multiplet $C\underline{H}_2$—NH_2), 3.0 (1H, multiplet $C\underline{H}$—CH_2NH_2) 0.9—1.7 (10H multiplet-aliphatic cyclohexyl ppm.

Mass Spectral Analysis by Chemical Ionization: 220 $(M+H)^+$ (Mol. Wt. 219) (free base).

Example 6

1-(α[(Dimethylamino)methyl]benzyl)-cyclohexanol

1-[α-(aminomethyl)benzyl]cyclohexanol (1.38 g, 0.006 mole) was dissolved in a mixture of formaldehyde (2 ml) formic acid (2.6 ml) and water (25 ml), and refluxed at 95°C. for 18 hours. The reaction mixture was cooled basified with solid KOH and extracted with methylene chloride. The extract was washed with brine, dried over magnesium sulphate and evaporated. The hydrochloride (m.p. 225—227°C)

was prepared using 3N-iso-propanolic HCl. Yield 589 mg.

Analysis for: $C_{16}H_{25}NO{\cdot}HCl$

Calculated: C, 67.36; H, 9.12; N, 4.88%

Found: C, 67.7; H, 9.23; N, 4.93%.

Mass Spectral Analysis: Molecular weight 247 (M^+, free base).

N.M.R. Analysis: (DMSO) δ 7.4 (5H, singlet, aromatic), 3.68 (2H, multiplet $C\underline{H}_2$—N $(CH_3)_2$, 3.18 (1H, multiplet $C\underline{H}CH_2N(CH_3)_2$ 2.68 (6H, $N(C\underline{H}_3)_2$; 0.9—1.7 (10H multiplet aliphatic cyclohexyl) ppm.

Example 7

1-(α[(Methylamino)methyl]benzyl)cyclohexanol

1-[α-(aminomethyl)benzyl]cyclohexanol (1.59 g., 0.007 mole) was dissolved in diethyl ether (10 ml.) and cooled to 5°C. Trifluoroacetic anhydride (2G) was added and the mixture stirred at 0°C for 30 minutes. The mixture was neutralized using saturated sodium bicarbonate solution and the layers separated. The organic layer was washed with brine, dried over magnesium sulphate and evaporated. A crystalline trifluoroacetamide m.p. 78—80°C. was obtained (975 mg.).

The trifluoroacetamide (975 mg.) was dissolved in dry acetone (20 ml.) and treated with methyl iodide (2 g.). The solution was warmed to reflux temperature and dry powdered potassium hydroxide (1 g.) added, followed by excess methyl iodide. The mixture was refluxed for five minutes, then cooled and the acetone evaporated. Water (20 ml.) was added and the mixture refluxed for 15 minutes. It was cooled and extracted with ethyl acetate. The extract was washed with water and brine, dried over magnesium sulfate and evaporated to a crystalline product m.p. 92—94°C. This was converted to the hydrochloride using 3N-isopropanolic HCl. Yield 235 mg., m.p. 208—210°C.

N.M.R. Analysis ($CHCl_3$), δ 7.3 (7H, aromatic, *H*Cl and $N\underline{H}{\cdot}CH_3$); 3.9 (1H multiplet $C\underline{H}$—CH_2NH_2); 3.25 (2H multiplet $C\underline{H}_2$—NH_2); 2.6 (3H singlet NH—$C\underline{H}_3$); 0.8—1.9 (10H multiplet, aliphatic cyclohexyl) ppm.

Mass Spectral Analysis: Molecular weight by chemical ionization/M.S. 233 (M + 1 at 234, free base).

Example 8

1-(α-[(Dimethylamino)methyl]benzyl)cyclohexanol acetate

1-(α-[(Dimethylamino)methyl]benzyl)cyclohexanol, (0.5 g., 0.0025 mole) was treated with acetic anhydride (1 ml.) and pyridine (3 ml.) and the mixture stood at room temperature overnight. The reaction mixture was poured into water, basified with solid KOH and extacted with ethyl acetate. The extract was washed with water and brine, dried over magnesium sulphate and evaporated to an oil. After azetropic distillation with toluene to remove traces of pyridine, the oil was treated with 3N isopropanolic HCl and crystalline hydrochloride as the title compound was obtained (70 mg.) m.p. 163—165°C.

NMR Analysis: ($CHCl_3$) δ 7.35 (5H singlet, aromatic); 4.2 (1H multiplet $C\underline{H}CH_2N(CH_3)2$; 3.6 (2H multiplet $C\underline{H}_2$—$N(CH_3)_2$); 2.65 (6H singlet, $N(CH_3)_2$); 2.1 (3H singlet, —O—$C\underline{H}_3$); 0.9—1.7 (10H multiplet, aliphatic cyclohexyl) ppm.

Mass Spectral Analysis: Molecular weight 289 (M^+, free base).

Example 9

1-[cyano(p-chlorophenyl)methyl]cyclohexanol

By replacing the p-methoxyphenyl acetonitrile in Example 1 by a molar equivalent amount of p-chlorophenyl acetonitrile, there was obtained 1-cyano(p-chlorophenyl)methyl cyclohexanol (13.7 g.) m.p. 115—117°.

Mass Spectral Analysis: Molecular weight 249 $(M+1)^+$ by C.I.M.S

Example 10

1-[2-amino-1-(4-chlorophenyl)ethyl]cyclohexanol

Lithium aluminum hydride (3.5 g.) was suspended in ice cold tetrahydrofuran (125 ml.) and concentrated sulphuric acid (2.5 ml.) added cautiously, with stirring. After one hour, 1-[cyano(p-chlorophenyl)methyl]cyclohexanol (15 g., 0.06 mole) was dissolved in tetrahydrofuran (100 ml.) and added rapidly dropwise with vigorous stirring and cooling. After a further two hours, a tetrahydrofuran-water mixture (1:1; 30 ml.) was added followed by 10% sodium hydroxide solution (50 ml.). The tetrahydrofuran was decanted and the residue washed well with diethyl ether and ethylacetate. The combined organic solution was dried over anhydrous potassium carbonate and evaporated to an oil (12 g).

Mass Spectral Analysis: Molecular weight 253 $(M+1)^+$ by C.I.M.S.

Example 11

1-[1-(4-chlorophenyl)-2-(dimethylamino)ethyl]cyclohexanol

1-[2-amino-1-(4-chlorophenyl)ethyl]cyclohexanol (12 g., 0.04 mole) was treated with a mixture of formaldehyde (13.7 ml.) formic acid (18.1 ml.) and water (160 ml) and refluxed at 100°C. for four hours. The reaction mixture was cooled extracted well with ethylacetate and the extract discarded. The aqueous residue was cooled in ice and rendered basic by the addition of solid potassium hydroxide, saturated with sodium chloride and thrice extracted with ethyl acetate. The extract was washed with brine, dried over

anhydrous potassium carbonate and evaporated. A crystalline solid (3 g.) was filtered. It was converted to the hydrochloride salt using 4N-isopropanolic HCl; yielding 4.7 g., m.p. 241—243°C.

Mass Spectral Analysis: Molecular weight 281 $(M+1)^+$ by C.I.M.S.

NMR analysis: δ 7.35 (4*H* singlet characteristic of 4-chloro substitution) 3.65 (2*H* multiplet, $C\underline{H}_2$—$CHN(CH_3)_2$), 3.0 (1*H* multiplet $CH_2C\underline{H}N(CH_3)_2$ 1.4 (10*H* multiplet, aliphatic cyclohexyl) ppm.

Example 12

1-[1-(4-methoxyphenyl)-2-(methylamino)ethyl]cyclohexanol

By replacing 1-α-(aminomethyl)benzyl]cyclohexanol with a molar equivalent amount of 1-[2-amino-1-(p-methoxyphenyl)ethyl] cyclohexanol in Example 7, 1-[1-(4-methoxyphenyl)-2-(methylamino)ethyl]cyclohexanol hydrochloride (m.p. 164—166°C.) was obtained.

Mass Spectral Analysis: Molecular weight 263 $(M+1)^+$ by C.I.M.S.

NMR analysis: δ 7.28 6.92 (4H quartet, p-substituted aromatic) 3.76 (3H singlet, OMe) 3.4 (2*H* multiplet, $C\underline{H}$—$CHN(CH_3)_2$) 2.9 (1*H* multiplet, $CH_2C\mathit{H}N(CH_3)_2$) 2.54 (3H, NCH_3) 1.4 (10*H* broad multiplet, aliphatic cyclohexyl) ppm.

Example 13

4-bromo-N,N-dimethylbenzene acetamide

Para-bromophenylacetic acid (50 g., 0.233 mole) was dissolved in methylene chloride (500 ml) and treated with oxalyl chloride (23.3 ml., 0.27 mole) and D.M.F. (0.5 ml) at room temperature. The mixture was stirred for four hours until gas evolution ceased. The solvent was evaporated and the residue dried under vacuum to remove excess oxalyl chloride. The residue ws dissolved in methylene chloride (300 ml) and treated with an excess of gaseous dimethylamine. The mixture was stirred overnight and the solvent evaporated. The residue was redissolved in methylene chloride and the solution washed with saturated sodium bicarbonate solution, N-hydrochloric acid, water, brine, dried over magnesium sulphate and evaporated. The buff-colored crystals were filtered with hexane and air-dried. Yield 51.2 g., m.p. 73—76°C.

Analysis for: $C_{10}H_{12}NOBr$

Calculated: C, 49.59; H, 4.96; N, 5.79

Found: C, 48.98; H, 5.14; N, 5.77

NMR Analysis ($CHCl_3$): δ 7.55 (4H quartet, aromatic) 3.65 (2H singlet) 2.95 (6H singlet, $N(CH_3)_2$) ppm.

Example 14

1-[(4-bromophenyl([dimethylamino)carbonyl]methyl]cyclohexanol

4-bromo-N,N-dimethylbenzyl acetamide (15 g., .06 mole) was added to dry T.H.F. (250 ml) and the solution cooled to —78°C under nitrogen. Straight chain butyl lithium in hexane (43.3 ml, 0.06 mole) was added dropwise, the temperature being maintained below −70°C throughout. An orange coloured precipitate formed. After addition, the reaction mixture was maintained near −70°C for 20 minutes and cyclohexanone (7.5 ml, 0.07 mole) was added. After a further 50 minutes at −78°C the reaction mixture was poured into stirred saturated ammonium chloride solution. The layers were separated and the aqueous layer extracted with diethyl ether. The combined organic solution was washed with brine, dried over magnesium sulfate and evaporated. The product crystallised and was filtered with isopropanol (9.8 g., m.p. 140—144°C).

Analysis for: $C_{16}H_{22}NO_2Br$

Calculated: C, 56.47; H, 6.47; N, 4.12

Found: C, 57.22; H, 6.66; N, 4.21

NMR Analysis ($CHCl_3$) δ 7.35 (4H, aromatic) 3.63 (1H singlet $C\underline{H}$—$CON(CH_3)_2$) 2.95 (6H singlet, N—$(CH_3)_2$); 1.45 (10H multiplet, aliphatic cyclohexyl) ppm.

Example 15

1-[1-(4-bromophenyl)-2-(dimethylamino)ethyl]cyclohexanol

Lithium aluminum hydride (0.7 g.) was suspended in dry THF (25 ml) cooled to 0°C and concentrated sulfuric acid (0.5 ml) cautiously added in an *in situ* preparation of aluminum hydride. The mixture was stirred for one hour at 0°C and the amide, 1-[(4-bromophenyl)]dimethylaminocarbonyl]methyl]-cyclohexanol (4 g., 0.012 mole) was dissolved in THF (35 ml) and added rapidly dropwise. The reaction mixture was stirred at 0°C for one hour. A THF-water mixture (1:1 v/v 6 ml) was added slowly followed by 10% sodium hydroxide (10 ml). The mixture was filtered and the residue washed well with ethyl acetate. The combined filtrate was dried over anhydrous potassium carbonate and evaporated to an oil (3.5 g) which was converted to the hydrochloride salt using 4 N isopropanolic HCl.

Analysis for: $C_{16}H_{24}NOBr \cdot HCl$

Calculated: C, 52.97; H, 6.9; N, 3.86

Found: C, 52.71; H, 6.63; N, 3.71

NMR analysis: (DMSO) δ 7.4 (4H, aromatic) 3.55 (2H doublet CH—$C\underline{H}_2N(CH_3)_2$); 3.05 (1H, triplet, $C\underline{H}$—$CH_2N(CH_3)_2$); 2.63 (6H singlet, N—$(CH_3)_2$) 1.30 (10H multiplet, aliphatic cyclohexyl) ppm.

Example 16

1-[1-(3-bromophenyl)-2-(dimethylamino)ethyl]cyclohexanol

By replacing p-bromophenyl acetic acid with a molar equivalent amount of m-bromophenyl acetic acid in Example 13, and following procedures described in Examples 14 and 15, 1-[1-(3-bromophenyl)-2-(dimethylamino)ethyl]cyclohexanol was obtained as the hydrochloride, m.p. 198—201°C.

Analysis for: $C_{16}H_{24}NOBr \cdot HCl$

Calculated: C, 52.97; H, 6.90; N, 3.86

Found: C, 52.84; H, 6.92; N, 3.99

Example 17

1-[1-(3-chlorophenyl)-2-(dimethylamino)ethyl]cyclohexanol

By replacing p-bromophenyl acetic acid with a molar equivalent amount of m-chlorophenylacetic acid in Example 13, and following procedures described in Examples 14 and 15, 1-[1-(3-chlorophenyl)-2-(dimethylamino)ethyl]cyclohexanol was obtained as the hydrochloride, m.p. 214—216°C.

Analysis for: $C_{16}H_{24}NOCl \cdot HCl$

Calculated: C, 60.38; H, 7.86; N, 4.4

Found: C, 60.07; H, 7.79; N, 3.93

Example 18

1-[1-(2-chlorophenyl)-2-(dimethylamino)ethyl]cyclohexanol

By replacing p-bromophenyl acetic acid with a molar equivalent amount of o-chlorophenylacetic acid in Example 13, and following procedures described in Examples 14 and 15, 1-[1-(2-chlorophenyl)-2-(dimethylamino)ethyl]cyclohexaol was obtained as the hydrochloride, m.p. 205—206°C.

Analysis for: $C_{16}H_{24}NOCl \cdot HCl$

Calculated: C, 60.38; H, 7.86; N, 4.4

Found: C, 60.45; H, 7.71; N, 4.79

Example 19

1-[1-(3,4-dichlorophenyl)-2-(dimethylamino)ethyl]cyclohexanol

By replacing p-bromophenyl acetic acid with a molar equivalent amount of 3,4-dichlorophenylacetic acid in Example 13, and following procedures described in Examples 14 and 15, 1-[1-(3,4-dichlorophenyl-2-(dimethylamino)ethyl]cyclohexanol was obtained as the hydrochloride, m.p. 241—244°C.

Analysis for: $C_{16}H_{23}NOCl_2 \cdot HCl$

Calculated: C, 54.47; H, 6.81; N, 3.97

Found: C, 54.8; H, 6.83; N, 3.99

Example 20

1-[1-(3,4-dichlorophenyl)-2-(dimethylamino)ethyl]cyclohexanol

The product of the preceding example is similarly produced by the following procedure:

Lithium diisopropylamide was prepared by dissolving di-isopropylamine (69 ml) in THF (500 ml) followed by the addition of n-butyllithium (325 ml). After 10 minutes stirring, the straw colored liquid was cooled to −78°C and 3,4-dichloro-N,N-dimethylbenzene acetamide (110.9 g, crude) was dissolved in 300 ml THF and added slowly. A dark red slurry was obtained. The mixture was stirred for a further 20 minutes and cyclohexanone (55.7 ml) was added. After 60 minutes at −78°C the reaction mixture was poured into a saturated solution of ammonium chloride. The aqueous layer was extracted with diethyl ether and the combined organic solution was washed with brine, dried over K_2CO_3 and evaporated. The product, 1-[(3,4-dichlorophenyl)(dimethylaminocarbonyl)methyl]cyclohexanol, crystallized and was filtered. The crystals were washed with isopropanol and with petroleum ether and air dried. Yield: 73.6 g., m.p. 118—120°C.

To an ice cold solution of Borane THF complex (152 ml. 152 mmole) was added a solution of 1-[(3,4-dichlorophenyl)(dimethylaminocarbonyl)methyl]cyclohexanol (30 g, 90 mmole) in THF. The mixture was refluxed for 2 hours and cooled again in an ice bath. 2N HCl (23 ml) was added and the mixture refluxed for 1.5 hours. It was cooled overnight. The reaction mixture was basified to pH 14 with solid potassium hydroxide and the layers were separated. The organic layer was washed with brine, dried over magnesium sulfate and evaporated to a solid. This was filtered and washed with diethyl ether and air dried. Yield: 15.4 g.; m.p. 128—130°C.

This product was converted to the hydrochloride which was identical with the product in Example 19.

Example 21

1-[2-(dimethylamino)-1-(3-methoxyphenyl)ethyl]cyclohexanol

By replacing p-bromophenyl acetic acid with a molar equivalent amount of m-methoxyphenyl acetic acid in Example 13, and following procedures described in Examples 14 and 15, 1-[2-(dimethylamino)-1-(3-methoxyphenyl)ethyl]cyclohexanol was obtained as the hydrochloride, m.p. 166—168°C.

Analysis for: $C_{16}H_{25}NO_2 \cdot HCl$
Calculated: C, 64.11; H, 8.68; N, 4.67
Found: C, 63.12; H, 8.54; N, 4.46

Example 22

1-[1-(3,4-dimethoxyphenyl)-2-(dimethylamino)ethyl]cyclohexanol

By replacing p-bromophenyl acetic acid with a molar equivalent amount of 3,4-dimethoxyphenyl acetic acid in Example 13, and following procedures described in Examples 14 and 15, 1-[1-(3,4-dimethoxyphenyl)-2-(dimethylamino)ethyl]cyclohexanol was obtained as the hydrochloride.

Analysis for: $C_{18}H_{29}NO_3 \cdot HCl$
Calculated: C, 62.88; H, 8.74; N, 4.08
Found: C, 62.42; H, 8.56; N, 3.98

Example 23

1-[2-(dimethylamino)-1-(4-trifluoromethylphenyl)ethyl]cyclohexanol

By replacing p-bromophenyl acetic acid with a molar equivalent amount of p-trifluoromethylphenyl acetic acid in Example 13, and following procedures described in Examples 14 and 15, 1-[2-(dimethylamino)-1-(4-trifluoromethylphenyl)ethyl]cyclohexanol was obtained as the hydrochloride, m.p. 238—240°C.

Analysis for: $C_{17}H_{25}NOF_3 \cdot HCl$
Calculated: C, 58.03; H, 7.16; N, 3.98
Found: C, 58.47; H, 7.16; N, 4.07

Example 24

1-[2-(dimethylamino)-1-(3-trifluoromethylphenyl)ethyl]cyclohexanol

By replacing p-bromophenyl acetic acid with a molar equivalent amount of m-trifluoromethylphenyl acetic acid and Example 13, and following procedures described in Examples 14 and 15, 1-[2-(dimethylamino)-1-(3-trifluoromethylphenyl)ethyl]cyclohexanol was produced as the hydrochloride, m.p. 194—196°C.

Analysis for: $C_{17}H_{25}NOF_3 \cdot HCl$
Calculated: C, 58.03; H, 7.16; N, 3.98
Found: C, 58.31; H, 7.09; N, 4.09

Example 25

1-[2-(dimethylamino)-1-(4-mehtylphenyl)ethyl]cyclohexanol

By replacing p-bromophenyl acetic acid with a molar equivalent amount of p-methylphenyl acetic acid in Example 13, and following procedures described in Examples 14 and 15, 1-[2-(dimethylamino)-1-(4-methylphenyl)ethyl]cyclohexanol was produced as the hydrochloride.

Analysis for: $C_{17}H_{17}NO \cdot HCl$
Calculated: C, 68.54; H, 9.17; N, 4.70
Found: C, 68.37; H, 9.31; N, 4.83

Example 26

1-[2-(dimethylamino)-1-(4-hydroxyphenyl)ethyl]cyclohexanol

By replacing p-bromophenyl acetic acid with a molar equivalent amount of p-benzyloxyphenyl acetic acid in Example 13, and following the procedures described in Examples 14 and 15, 1-[1-(4-benzyloxyphenyl)-2-(dimethylamino)ethyl]cyclohexanol was obtained.

Hydrogenolysis of this product to remove the benzyl protecting group from the 4-hydroxyphenyl moiety was accomplished by dissolving 1.0 grams of the product in 100 ml. ethanol. One gram, 10% Pd/C was introduced followed by cyclohexa-1,4-diene (5 ml.). The mixture was stirred for ninety minutes at ambient temperature. The catalyst was removed by filtration and the solvent removed by evaporation to yield 800 mg. of solid. This solid 4-hydroxyphenyl product was converted to its fumarate salt via an acetone-ethanol solution, m.p. 140—142°C.

Analysis for: $C_{16}H_{25}NO_2 \cdot C_4H_4O_4$
Calculated: C, 63.30; H, 7.70; N, 3.69
Found: C, 62.18; H, 7.90; N, 3.63

Example 27

1-[2-(dimethylamino)-1-(3-hydroxyphenyl)ethyl]cyclohexanol

By replacing p-bromophenyl acetic acid with a molar equivalent amount of m-benzyloxyphenyl acetic acid in Example 13, and following the procedures described in Examples 14 and 15, 1-[1-(3-benzyloxyphenyl)-2-(dimethylamino)ethyl]cyclohexanol was obtained.

Hydrogenolysis of this product (2.3 g) was conducted in 200 ml ethanol employing a Paar bomb, 300 mg. 10% Pd/C until up-take of hydrogen ceased. The catalyst was removed by filtration and the solvent evaporated to afford a solid product which was converted to its hydrochloride salt with 5 N isopropanolic HCl m.p. 162—164°C.

Analysis for: $C_{16}H_{25}NO_2 \cdot HCl$
Calculated: C, 64.08; H, 8.74; N, 4.67
Found: C, 62.78; H, 8.55; N, 4.55

Example 28

1-[1-(4-bromophenyl)-2-(dimethylamino)ethyl]cyclobutanol

By replacing cyclohexanone in Example 14 with a molar equivalent amount of cyclobutanone and following the procedure described in Example 15, 1-[1-(4-bromophenyl)-2-(dimethylamino)ethyl]cyclobutanol was obtained. It was converted to the hydrochloride salt, m.p. 220—222°C.

Analysis for: $C_{14}H_{20}NOBr \cdot HCl$
Calculated: C, 50.22; H, 6.28; N, 4.19
Found: C, 50.26; H, 6.11; N, 4.13

Example 29

1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclopentanol

By replacing p-bromophenylacetic acid with a molar equivalent amount of p-methoxyphenyl acetic acid in Example 13, 4-methoxy-N,N-dimethylbenzene acetamide was obtained. Subsequently, following the procedure outlined in Example 14, replacing cyclohexanone with a molar equivalent amount of cyclopentanone, there was obtained the corresponding cyclopentanol derivative. This intermediate was converted, following the procedure described in Example 15, to the title compound as the hydrochloride, m.p. 194°C.

Analysis for: $C_{16}H_{25}NO_2 \cdot HCl$
Calculated: C, 64.07; H, 8.76; N, 4.67
Found: C, 64.19; H, 8.72; N, 4.33

Example 30

1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cycloheptanol

By replacing cyclopentanone with a molar equivalent of cycloheptanone in Example 27, the title compound was obtained as the hydrochloride, m.p. 175—177°C.

Analysis for: $C_{18}H_{29}NO_2 \cdot HCl \cdot 1/4H_2O$
Calculated: C, 65.03; H, 9.26; N, 4.21
Found: C, 65.25; H, 9.16; N, 4.29

Example 31

1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclooctanol

By replacing cyclopentanone with a molar equivalent of cyclooctanone in Example 29, the title compound was obtained as the hydrochloride, m.p. 178—180°C.

Analysis for: $C_{19}H_{31}NO_2 \cdot HCl \cdot 1/4H_2O$
Calculated: C, 65.87; H, 9.48; N, 4.04
Found: C, 65.79; H, 9.08; N, 3.95

Example 32

1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]-cyclohex-2-en-1-ol

By replacing 4-bromo-N,N-dimethylbenzeneacetamide with a molar equivalent of 4-methoxy-N,N-dimethylbenzeneacetamide in Example 14, and cyclohexanone with 2-cyclohexen-1-one, was obtained the corresponding cyclohexenone derivative. This intermediate was converted following the procedure described in Example 15 to the title compound as the furmarate, m.p. 128—130°C.

Analysis for: $C_{17}H_{25}NO_2 \cdot C_4H_4O_4$
Calculated: C, 64.4; H, 7.31; N,3.58
Found: C, 63.8; H, 7.46; N,3.88

Example 33

Resolution of Racemic 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol

1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol (48.0 g, 0.173 m) dissolved in ethyl acetate (350 ml) was treated with di-p-toluoyl-d-tartaric acid (33.5 g, 0.082 m) dissolved in ethyl acetate (250 ml). After standing overnight, the solid was filtered. The solid was recrystallized three times by dissolving in boiling ethyl acetate (300 ml) and methanol (50 ml), concentrating by boiling to incipient crystallization and chilling. Yield 31.7 g, m.p. 126—128°C. $[\alpha]_D^{25} = -50.51$; c = 1.03 ethanol.

The salt was converted to its free base by shaking in 2N sodium hydroxide and diethyl ether. The ether layer was washed with brine, dried over anhydrous sodium carbonate, evaporated and dried *in vacuo*. Yield 16.4 g, 68.5%, m.p. 104—5°C. $[\alpha]_D^{25} = +27.95$; c = 1.15, 95% ethanol.

The base was dissolved in ether (500 ml) and treated with 4.5N hydrogen chloride in isopropanol (20 ml). The resulting hydrochloride salt was recrystallized from warm methanol (75 ml) by dilution with ether (400 ml) and chilling. Yield 16.6 g, m.p. 239—241°C. $[\alpha]_D^{25} = -4.38$; c = 1.01, 95% ethanol.

The filtrate and washings from the original di-p-toluoyl-d-tartrate salt were evaporated to dryness. The free base was obtained by shaking the solid with 2N sodium hydroxide (400 ml), extracting with diethyl ether (3 x 250 ml), washing the extracts with brine and drying. Yield 24.2 g. The base was dissolved in ethyl acetate (150 ml) and treated with di-p-toluoyl-1-tartaric acid (16.75 g, 0.0435 m) dissolved in ethyl acetate (150 ml). After standing overnight the salt was filtered and was recrystallized twice from ethyl acetate (300 ml) and methanol (50 ml) as described. Yield 29.4 g, m.p. 124—127°C. $[\alpha]_D^{25} = +50.77$, c = 0.845 ethanol.

The base was obtained in the manner described. Yield 14.7 g, m.p. 104—105°C. $[\alpha]_D^{25} = -26.56$, c = 1.22%, 95% ethanol.

The free base was converted to the hydrochloride salt. Yield 14.5 g, m.p. 239—241°C. $[\alpha]_D^{25} = +4.98$, c = 1.01, 95% ethanol.

Example 34

1-[1-(4-aminophenyl)-2-dimethylaminoethyl]cyclohexanol

17.0 g (0.095 moles) of p-aminophenylacetic acid. dimethylamide was dissolved in 500 ml of tetrahydrofuran, placed under a nitrogen atmosphere, and cooled to −20°C. 23.6 g (1.15 equivalents) of 1,1,4,4-tetramethyl-1,4-dichlorosilylethylene was added, followed dropwise by a solution of 42 g (2.4 equivalents) of sodium bis(trimethylsilyl)amide in 250 ml of THF. The mixture was allowed to warm to room temperature and was stirred for 18 hours.

The mixture was next cooled to −78°C and 71.6 ml (1.2 equivalents) of 1.6 N n-butyl lithium in hexane added. The reaction was stirred for 45 minutes and then 20 ml (2.0 equivalents) of cyclohexanone added. The mixture was stirred for an additional 1 hour at −78°C and then poured into a saturated aqueous solution of ammonium chloride. The organic phase was removed and the aqueous phase was extracted with diethyl ether. The combined organic phases were dried over sodium sulphate, filtered and concentrated *in vacuo* to yield 20 g of crude 1-[(4-aminophenyl)(dimethylaminocarbonyl)methyl]cyclohexanol. Column chromatography on silica gel with 1% methanol in methylene chloride gave 16 g of essentially pure white solid. A sample twice recrystallized from ethanol had m.p. 169—170°C and the following elemental analysis:

Analysis for: $C_{16}H_{24}O_2N_2$

Calculated: C, 69.51; H, 8.77; N, 10.14

Found: C, 69.69; H, 8.96; N, 10.26

5.0 g (0.018 mole) of the above amide was dissolved in 300 ml of dry tetrahydrofuran and added dropwise to a mixture of 1.1 g of lithium aluminum hydride and 8.0 ml of concentrated sulfuric acid in 200 ml of tetrahydrofuran at 0°C. The mixture was stirred at 0°C for five hours, then the excess reagent was destroyed by the dropwise addition of 4 ml of 50:50 THF-water, then 4 ml of 15% aqueous sodium hydroxide and finally 4 ml of water. The mixture was filtered and the precipitate washed several times with THF. The combined filtrates were evaporated and the residue recrystallized from isopropanol to give 3.8 g of the title compound as the free base. Treatment with excess oxalic acid in ethyl acetate gave the dioxalate, m.p. 105°C(d).

Analysis for: $C_{20}H_{30}N_2O_9$

Calculated: C, 55.28; H, 6.84; N, 6.33

Found: C, 53.96; H, 6.83; N, 6.24

Example 35

1-[1-(4-nitrophenyl)-2-dimethylaminoethyl]cyclohexanol

2.0 g (7.6 mmoles) of 1-[1-(4-aminophenyl)-2-dimethylaminoethyl]cyclohexanol was dissolved in 50 ml of methylene chloride and added dropwise to a stirred solution of 2.2 g (2.5 equivalents) of nitrosonium tetrafluoroborate. The reaction was stirred at room temperature for four hours. The methylene chloride was then removed *in vacuo* and replaced with 100 ml of water. This solution was added slowly to a mixture of 2.0 g of copper in 200 ml of 1 N sodium nitrite and the combination stirred for 2 hours at room temperature. Extraction with methylene chloride, drying, and evaporation *in vacuo* yielded 2.0 g of the free

base of the title compound. Recrystallization from isopropanolic HCl gave the hydrochloride, m.p. 211—212°C.

Analysis for: $C_{16}H_{24}O_3N_2$
Calculated: C, 58.42; H, 7.37; N, 8.52
Found: C, 58.03; H, 7.53; N, 8.69

Example 36

1-[2-(dimethylamino)-1-(3-bromo-4-methoxyphenyl)ethyl]cyclohexanol

By replacing 1-[2-amino-1-(p-methoxyphenyl)ethyl]cyclohexanol in Example 3 with a molar equivalent amount of 1-[2-amino-1-(3-bromo-4-methoxyphenyl)ethyl)cyclohexanol and refluxing overnight, the title compound was obtained, m.p. 218—220°C.

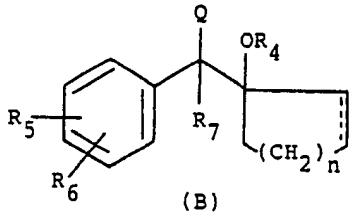
Analysis for: $C_{17}H_{26}NO_2BR \cdot HCl$
Calculated: C, 57.98; H, 6.92; N, 3.56
Found: C, 51.57; H, 6.79; N, 3.46

Example 37

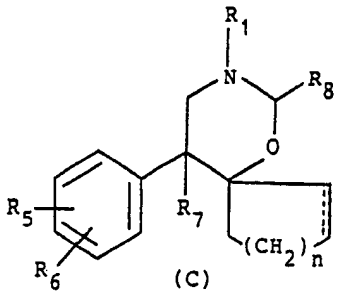
By following a procedure similar to Examples 13 to 15, using (a) 3,4-dibromophenylacetic acid, (b) 3-methylphenylacetic acid, (c) 4-bromophenylacetic acid and (d) 3-methoxyphenylacetic acid instead of p-bromophenylacetic acid and, as the cycloalkanone, (a) cyclohexanone, (b) cyclohexanone, (c) cyclobutanone and (d) cyclopentanone, there are prepared (a) 1-[1-(3,4-dibromophenyl)-2-(dimethylamino)ethyl]cyclohexanol, (b) 1-[2-(dimethylamino)-1-(3-methylphenyl)ethyl]cyclohexanol, (c) 1-[1-(4-bromophenyl)-2-(dimethylamino)ethyl]cyclobutanol and (d) 1-[2-(dimethylamino)-1-(3-methoxyphenyl)ethyl)cyclopentanol.

The processes available for preparation of the compounds having formula I and the salts thereof may be summarised as follows (where the symbols R_1, R_2, R_4, R_5, R_6, R_7 and n and the dotted lines are as defined under formula I above except that under items (1), (2) and (3) below neither R_5 not R_6 is cyano, nitro or C_2—C_7 alkanamido):—

(1) Reduction of compounds having one of the formulae B and C



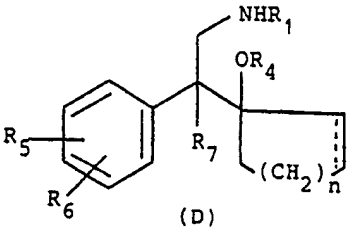
(B)



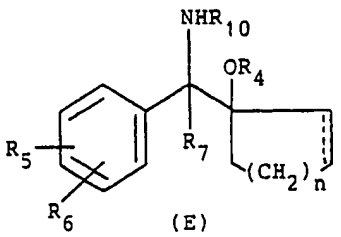
(C)

where Q is —$CONR_1R_2$; —$C = NR_1$; —$CH(OH)NR_1R_2$; —NR_1—COR_9; —N = CY_1Y_2 or —NR_1—CH(OH)—R_8; R_9 is alkoxy or C_1—C_5 alkyl, Y_1 and Y_2 are each selected from hydrogen and alkyl such that the group = CY_1Y_2 contains 1 to 6 carbon atoms; and R_8 is C_1—C_5 alkyl.

(2) (a) Reaction of a compound having formula D or E



(D)

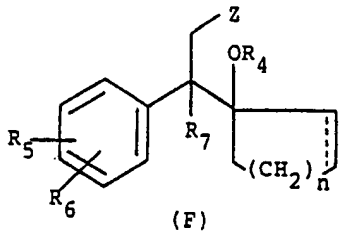


(E)

(where R_{10} is a readily splittable substituent, e.g. —$COCF_3$ or —R_6CO-alkoxy) with an alkylating agent to introduce one or two C_1—C_6 alkyl groups (if R_1 is H) or one such alkyl group and, if necessary, splitting off the said substituent; or

(b) Reaction of a compound having formula D with a carbonyl compound of formula Y_1Y_2CO [where Y_1 and Y_2 are as defined under item (1)] in the presence of a reducing agent.

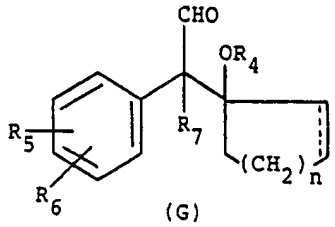
(3) (a) Reaction of a compound having formula NHR_1R_2 or NHR_2R_{10} (where R_{10} is as defined above) with a compound having the formula F



(F)

where Z is a leaving group (e.g. halogen or organosulphonyloxy) and, if necessary, splitting off the substituent R_{10}; or

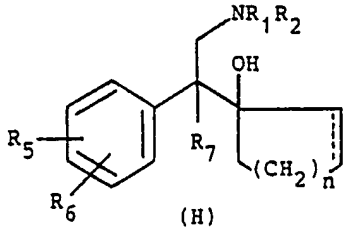
(b) Reaction of a compound having formula HNR_1R_2 with an aldehyde of formula G



(G)

in the presence of a reducing agent.

(4) Reaction of a compound having formula H



(H)

with a reactive derivative of formic acid or of a C_2—C_7 alkanoic acid to introduce formyl or C_2—C_7 alkanoyloxy as R_4.

(5) Reaction of a compound having formula I where R_5 and/or R_6 is amino by mono- or di-alkylation or acylation to form a compound having formula I where R_5 and/or R_6 is mono- or di(C_1—C_6alkyl)amino or C_2—C_7 alkanamido.

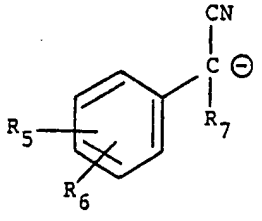
(6) Diazotizing a compound having formula I where R_5 and/or R_6 is amino and displacing the diazolate salt with a nitrite or cyanide to form a compound where R_5 and/or R_6 is nitro or cyano.

(7) Reaction of a compound having formula I where R_5 and/or R_6 is halo with a cyanide to displace the halo substituent with cyano.

(8) Formation of a compound having formula I or salt thereof by removal of a protecting group to give amino, N-(C_1—C_6 alkyl) amino or hydroxy as R_5 and/or R_6 or hydroxy as OR_4.

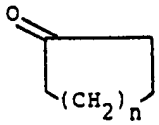
(9) Reaction of a compound having formula I with an acid to form a pharmaceutically acceptable salt thereof. The process available for the preparation of the new intermediates include:—

(10) Preparation of a compount (10) Preparation of a compound having formula IV by reaction of an anion having the formula J



(J)

(where R_5, R_6 and R_7 are as defined in formula IV) with a cycloalkanone having the formula K

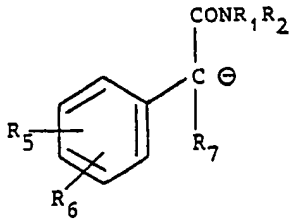


(K)

(where n is as defined under formula IV) and, if R_4 is C_1—C_4 alkyl, introducing the alkyl group by alkylation.

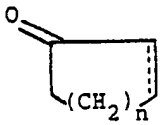
(11) Preparation of an amide having formula X where R_1 is alkyl of 1 to 6 carbon atoms by

(a) reacting an anion having the formula L



(L)

(where R_1, R_2, R_5, R_6 and R_7 have the same meanings as in formula X) with a cycloalkanone or cycloalkenone having formula M

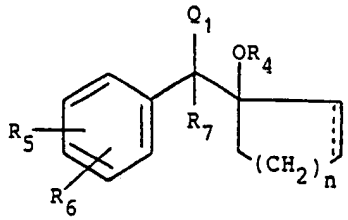


(M)

(where n and the dotted line have the same meaning as in formula X) and, if R_4 is C_1—C_4 alkyl, introducing the alkyl group by alkylation; or

(b) reacting an amine having the formula HNR_1R_2 (where R_1 and R_2 are as defined under formula X) with the acid halide derivative, active ester or anhydride of an acid having the formula XIV (where B is a carboxyl group and R_5, R_6, R_7, n and the dotted line are as defined under formula X).

(12) Preparation of a compound having formula VI by reduction of a compound having formula P

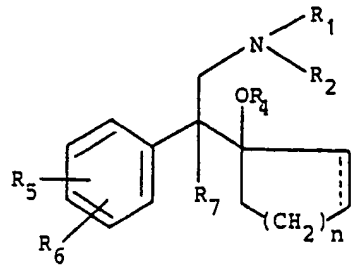


(P)

where R_4, R_5, R_7, n and the dotted line are as under formula VI and Q_1 is —CN, —CH_2—NO_2; —$CONH_2$ or —CH = N(OH) and where Q_1 is —CN R_5 and R_6 are as defined under formula IV.

Claims for the Contracting States: BE CH DE FR IT LI LU NL SE

1. A compound of the formula



(I)

in which the dotted line represents optional unsaturation;

R_1 is hydrogen or alkyl of 1 to 6 carbon atoms;

R_2 is alkyl of 1 to 6 carbon atoms;

R_4 is hydrogen, alkyl of 1 to 6 carbon atoms, formyl, or alkanoyl of 2 to 7 carbon atoms;

R_5 and R_6 are independently hydrogen, hydroxyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, cyano, nitro, alkylmercapto of 1 to 6 carbon atoms, amino, alkylamino of 1 to 6 carbon atoms, dialkylamino in which each alkyl group is of 1 to 6 carbon atoms, alkanamido of 2 to 7 carbon atoms, halo, trifluoromethyl, or, when taken together, methylene dioxy;

R_7 is hydrogen or alkyl of 1 to 6 carbon atoms; and n is 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt thereof.

2. A compound as claimed in Claim 1, in which

R_1 is hydrogen or alkyl of 1 to 3 carbon atoms;

R_2 is alkyl of 1 to 3 carbon atoms;

R_5 is hydrogen, hydroxy, alkoxy of 1 to 3 carbon atoms, chloro, bromo, trifluoromethyl or alkyl of 1 to 3 carbon atoms;

R_6 is alkyl of 1 to 3 carbon atoms, alkoxy of 1 to 3 carbon atoms, chloro, bromo, trifluoromethyl or alkanoyloxy of 2 to 3 carbon atoms;

R_7 is hydrogen or alkyl of 1 to 3 carbon atoms;

or a pharmaceutically acceptable salt thereof.

3. A compound as claimed in Claim 2 in which R_5 and R_6 are in meta or para positions and n is 2.

4. 1-[2-(Dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

5. A compound as claimed in Claim 4, whose configuration is such that the specific optical rotation of the free base form of the compound as measured in 95% ethanol at about 1% concentration at 25°C using the sodium D-line is positive.

6. A compound as claimed in Claim 4, whose configuration is such that the specific optical rotation of the free base form of the compound as measured in 95% ethanol at about 1% concentration at 25°C using the sodium D-line is negative.

7. 1-[2-(Dimethylamino)-1-(3-methoxyphenyl)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

8. 1-[2-[Dimethylamino)-1-(3-bromo-4-methoxyphenyl)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

9. 1-[2-(Dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohex-2-en-1-ol or a pharmaceutically acceptable salt thereof.

10. A compound selected from

1-(α-[(dimethylamino)methyl]benzyl)cyclohexanol;

1-(α-[(methylamino)methyl]benzyl)cyclohexanol;

1-(α-[(dimethylamino)methyl]benzyl)cyclohexanol acetate;

1-[1-(4-chlorophenyl)-2-(dimethylamino)ethyl] cyclohexanol;

1-[1-(4-methoxyphenyl)-2-(methylamino)ethyl] cyclohexanol;

1-[1-(4-bromophenyl)-2-(dimethylamino)ethyl] cyclohexanol;

1-[1-(3-bromophenyl)-2-(dimethylamino)ethyl] cyclohexanol;

1-[1-(3-chlorophenyl)-2-(dimethylamino)ethyl] cyclohexanol;

1-[1-(2-chlorophenyl)-2-(dimethylamino)ethyl] cyclohexanol;

1-[1-(3,4-dichlorophenyl)-2-(dimethylamino)ethyl] cyclohexanol;

1-[1-(3,4-dimethoxyphenyl)-2-(dimethylamino)ethyl] cyclohexanol;

1-[2-(dimethylamino)-1-(4-trifluoromethylphenyl)ethyl] cyclohexanol;

1-[2-(dimethylamino)-1-(3-trifluoromethylphenyl)ethyl] cyclohexanol;

1-[2-(dimethylamino)-1-(4-methylphenyl)ethyl] cyclohexanol;

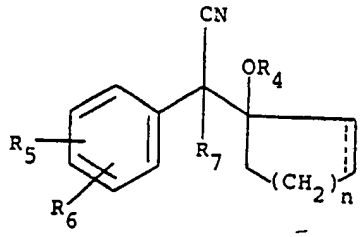
1-[2-(dimethylamino)-1-(4-hydroxyphenyl)ethyl] cyclohexanol;
1-[2-(dimethylamino)-1-(3-hydroxyphenyl)ethyl] cyclohexanol;
1-[1-(4-aminophenyl)-2-(dimethylamino)ethyl] cyclohexanol;
1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclopentanol;
1-[1-(4-nitrophenyl)-2-(dimethylamino)ethyl]cyclohexanol;
1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cycloheptanol;
1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclooctanol;
1-[1-(3,4-dibromophenyl)-2-(dimethylamino)ethyl]cyclohexanol;
1-[(2-dimethylamino)-1-(3-methylphenyl)ethyl]cyclohexanol;
1-[1-(4-bromophenyl)-2-(dimethylamino)ethyl]cyclobutanol;
1-[2-(dimethylamino)-1-(3-methoxyphenyl)ethyl]cyclopentanol;
1-[2-(dimethylamino)-1-(4-methoxyphenyl)-1-methylethyl]cyclohexanol and their pharmaceutically acceptable salts.

11. A pharmaceutical composition comprising a compound as claimed in any one of Claims 1 to 10 in association with a pharmaceutically acceptable carrier.

12. A pharmaceutical composition as claimed in Claim 11 in unit dosage form.

13. A compound as claimed in any one of Claims 1 to 10 for use as an antidepressant agent.

14. A compound having the formula



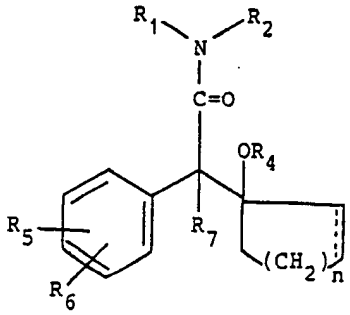
(IV)

in which R_4 is hydrogen or alkyl of 1 to 6 carbon atoms;

R_5 and R_6 are ortho or para substituents, independently selected from the group consisting of hydrogen, hydroxyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, aralkoxy of 7 to 9 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, alkylmercapto of 1 to 6 carbon atoms, halo and trifluoromethyl, subject to the proviso that R_5 and R_6 are not both hydrogen;

R_7 is hydrogen or alkyl of 1 to 6 carbon atoms; and n is 0, 1, 2, 3 or 4.

15. A compound having the formula



(X)

in which the dotted line represents optional unsaturation,

R_1 is hydrogen or alkyl of 1 to 6 carbon atoms;

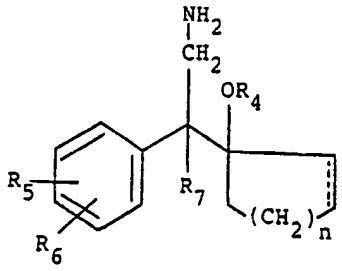
R_2 is alkyl of 1 to 6 carbon atoms;

R_4 is hydrogen or alkyl of 1 to 6 carbon atoms;

R_5 and R_6 are, independently, hydrogen, hydroxyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, aralkoxy of 7 to 9 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, alkylmercapto of 1 to 6 carbon atoms, N-protected amino, halo, trifluoromethyl, or when taken together, methylenedioxy, subject to the proviso that R_5 and R_6 are not both hydrogen;

R_7 is hydrogen or alkyl of 1 to 6 carbon atoms; and n is 0, 1, 2, 3 or 4.

16. A compound having the formula

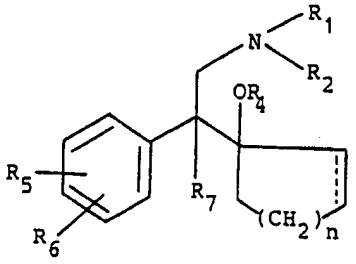


(VIa)

or a pharmaceutically acceptable salt thereof wherein the dotted line, R_4, R_5, R_6, R_7 and n are as defined in Claim 15.

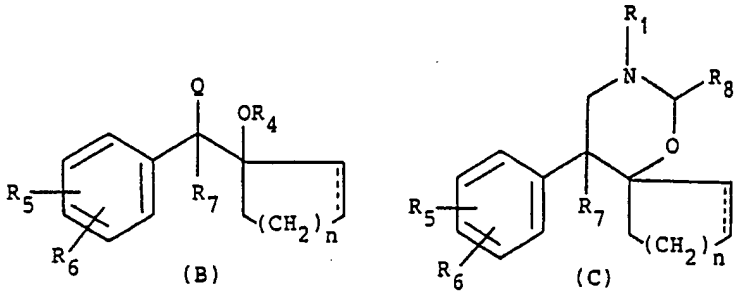
Claims for the Contracting State: AT

1. A process for the preparation of a compound of the formula



(I)

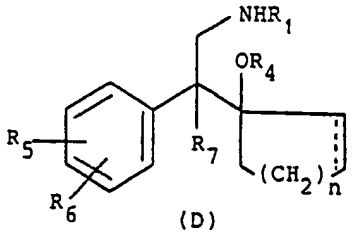
in which the dotted line represents optional unsaturation;
R_1 is hydrogen or alkyl of 1 to 6 carbon atoms;
R_2 is alkyl of 1 to 6 carbon atoms;
R_4 is hydrogen, alkyl of 1 to 6 carbon atoms, formyl, or alkanoyl of 2 to 7 carbon atoms;
R_5 and R_6 are independently hydrogen, hydroxyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, cyano, nitro, alkylmercapto of 1 to 6 carbon atoms, amino, alkylamino of 1 to 6 carbon atoms, dialkylamino in which each alkyl group is of 1 to 6 carbon atoms, alkanamido of 2 to 7 carbon atoms, halo, trifluoromethyl, or, when taken together, methylene dioxy;
R_7 is hydrogen or alkyl of 1 to 6 carbon atoms; and n is 0, 1, 2, 3 or 4;
or a pharmaceutically acceptable salt thereof; which comprises
(1) reduction of a compound having one of the formulae B and C



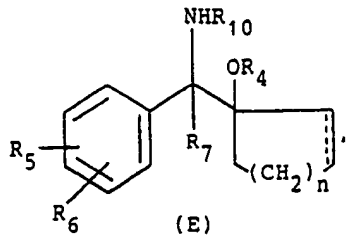
(B) (C)

where Q is $—CONR_1R_2$; $—C = NR_1$; $—CH(OH)NR_1R_2$; $—NR_1—COR_9$; $—N = CY_1Y_2$ or $—NR_1—CH(OH)—R_8$; R_9 is alkoxy or $C_1—C_5$ alkyl, Y_1 and Y_2 are each selected from hydrogen and alkyl such that the group $= CY_1Y_2$ contains 1 to 6 carbon atoms; and R_1, R_2, R_4, R_5, R_6, R_7 and n and the dotted lines are as defined under formula I save their neither R_5 nor R_6 is cyano, nitro or C_2 to C_7 alkanamido; or

(2) Reaction of a compound having formula D or E



(D)

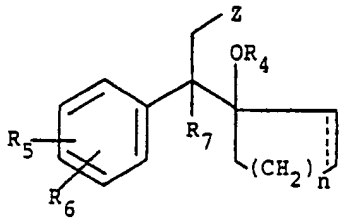


(E)

(where R_{10} is a readily splittable substituent, and R_1, R_5, R_6, R_7, n and the dotted line are as defined under formula I except that neither R_5 nor R_6 is cyano, nitro or C_2 to C_7 alkanamido) with an alkylating agent to introduce one or two C_1—C_6 alkyl groups (if R_1 is H) or one such alkyl group and, if necessary, splitting off the said substituent; or

(b) reaction of a compound having formula D as defined above with a carbonyl compound of formula Y_1Y_2CO [where Y_1 and Y_2 are as defined above] in the presence of a reducing agent; or

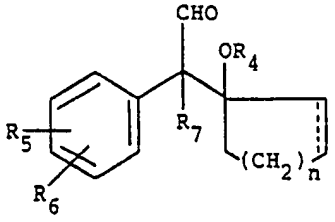
(3) (a) reaction of a compound having formula NHR_1R_2 or NHR_2R_{10} (where R_1, R_2 and R_{10} are as defined above) with a compound having the formula F



(F)

(where Z is a leaving group and R_5, R_6, R_7, n and the dotted line are as defined under formula I except that neither R_5 nor R_6 is cyano, nitro or alkanamido) and, if necessary, splitting off the substituent R_{10}; or

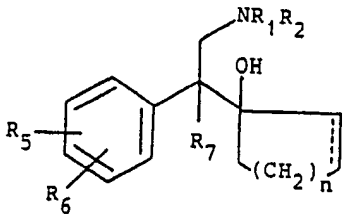
(b) reaction of a compound having formula HNR_1R_2 (where R_1 and R_2 are as defined above) with an aldehyde of formula G



(G)

(where R_4, R_5, R_6, R_7, the dotted line and n are as defined under formula I except that neither R_5 nor R_6 is cyano, nitro of C_2—C_7 alkanamido) in the presence of a reducing agent; or

(4) reaction of a compound having formula H



(H)

(where the dotted line, R_1, R_2, R_5, R_6, R_7 and n are as defined under formula I) with a reactive derivative of formic acid or of a C_2—C_7 alkanoic acid to introduce formyl or C_2—C_7 alkanoyloxy as R_4; or

(5) reaction of a compound having formula I where R_5 and/or R_6 is amino by mono- or di-alkylation or acylation to form a compound having formula I where R_5 and/or R_6 is mono- or di(C_1—C_6alkyl)amino or C_2—C_7 alkanamido; or

(6) diazotizing a compound having formula I where R_5 and/or R_6 is amino and displacing the diazolate

salt with a nitrite or cyanide to form a compound where R_5 and/or R_6 is nitro or cyano; or

(7) reaction of a compound having formula I where R_5 and/or R_6 is halo with a cyanide to displace the halo substituent with cyano; or

(8) formation of a compound having formula I or salt thereof by removal of a protecting group to give amino, N-(C_1—C_6 alkyl) amino or hydroxy as R_5 and/or R_6 or hydroxy as OR_4; or

(9) reaction of a compound having formula I with an acid to form a pharmaceutically acceptable salt thereof.

2. A process according to Claim 1, in which

R_1 is hydrogen or alkyl of 1 to 3 carbon atoms;

R_2 is alkyl of 1 to 3 carbon atoms;

R_5 is hydrogen, hydroxy, alkoxy of 1 to 3 carbon atoms, chloro, bromo, trifluoromethyl or alkyl of 1 to 3 carbon atoms;

R_6 is alkyl of 1 to 3 carbon atoms, alkoxy of 1 to 3 carbon atoms, chloro, bromo, trifluoromethyl or alkanoyloxy of 2 to 3 carbon atoms; and

R_7 is hydrogen or alkyl of 1 to 3 carbon atoms;

3. A process according to Claim 2, in which R_5 and R_6 are in meta or para positions and n is 2.

4. A process according to Claim 1, carried out so as to prepare 1-[2-(Dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

5. A process according to Claim 1, carried out so as to prepare 1-[2-(dimethylamino)-1-(3-methoxyphenyl)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

6. A process according to Claim 1, carried out so as to prepare 1-[2-[dimethylamino)-1-(3-bromo-4-methoxyphenyl)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

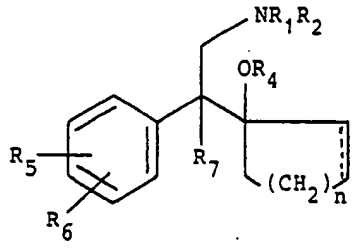
7. A process according to Claim 1, carried out so as to prepare 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohex-2-en-1-ol or a pharmaceutically acceptable salt thereof.

8. A process according to Claim 1, carried out so as to prepare a compound selected from

1-(α-[(dimethylamino)methyl]benzyl)cyclohexanol;
1-(α-[(methylamino)methyl]benzyl)cyclohexanol;
1-(α-[(dimethylamino)methyl]benzyl)cyclohexanol acetate;
1-[1-(4-chlorophenyl)-2-(dimethylamino)ethyl] cyclohexanol;
1-[1-(4-methoxyphenyl)-2-(methylamino)ethyl] cyclohexanol;
1-[1-(4-bromophenyl)-2-(dimethylamino)ethyl] cyclohexanol;
1-[1-(3-bromophenyl)-2-(dimethylamino)ethyl] cyclohexanol;
1-[1-(3-chlorophenyl)-2-(dimethylamino)ethyl] cyclohexanol;
1-[1-(2-chlorophenyl)-2-(dimethylamino)ethyl] cyclohexanol;
1-[1-(3,4-dichlorophenyl)-2-(dimethylamino)ethyl] cyclohexanol;
1-[1-(3,4-dimethoxyphenyl)-2-(dimethylamino)ethyl] cyclohexanol;
1-[2-(dimethylamino)-1-(4-trifluoromethylphenyl)ethyl] cyclohexanol;
1-[2-(dimethylamino)-1-(3-trifluoromethylphenyl)ethyl] cyclohexanol;
1-[2-(dimethylamino)-1-(4-methylphenyl)ethyl] cyclohexanol;
1-[2-(dimethylamino)-1-(4-hydroxyphenyl)ethyl] cyclohexanol;
1-[2-(dimethylamino)-1-(3-hydroxyphenyl)ethyl] cyclohexanol;
1-[1-(4-aminophenyl)-2-(dimethylamino)ethyl] cyclohexanol;
1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclopentanol;
1-[1-(4-nitrophenyl)-2-(dimethylamino)ethyl]cyclohexanol;
1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cycloheptanol;
1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclooctanol;
1-[1-(3,4-dibromophenyl)-2-(dimethylamino)ethyl]cyclohexanol;
1-[(2-dimethylamino)-1-(3-methylphenyl)ethyl]cyclohexanol;
1-[1-(4-bromophenyl)-2-(dimethylamino)ethyl]cyclobutanol;
1-[2-(dimethylamino)-1-(3-methoxyphenyl)ethyl]cyclopentanol;
1-[2-(dimethylamino)-1-(4-methoxyphenyl)-1-methylethyl]cyclohexanol and their pharmaceutically acceptable salts.

9. A process according to any one of Claims 1 to 8, wherein the compound prepared by the process is for use as a antidepressant agent.

10. A process for the preparation of a pharmaceutical composition having antidepressant activity, wherein a compound having the formula I

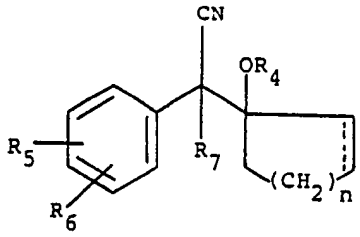


(I)

wherein R_1, R_2, R_5, R_6, R_7, n and the dotted lines are as defined under formula I in Claim 1, or a pharmaceutically acceptable salt thereof is brought into association with a pharmaceutically acceptable carrier.

11. A process according to Claim 10, wherein the composition is in unit dosage form.

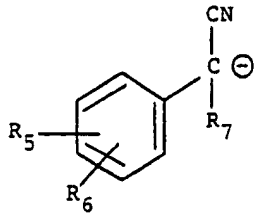
12. A process for the preparation of compound having the formula



(IV)

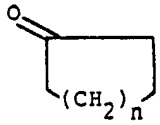
in which R_4 is hydrogen or alkyl of 1 to 6 carbon atoms; R_5 and R_6 are ortho or para substituents, independently selected from the group consisting of hydrogen, hydroxyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, aralkoxy of 7 to 9 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, alkylmercapto of 1 to 6 carbon atoms, halo and trifluoromethyl subject to the proviso that R_5 and R_6 are not both hydrogen;

R_7 is hydrogen or alkyl of 1 to 6 carbon atoms; and n is 0, 1, 2, 3, or 4; which comprises reaction of an anion having the formula J



(J)

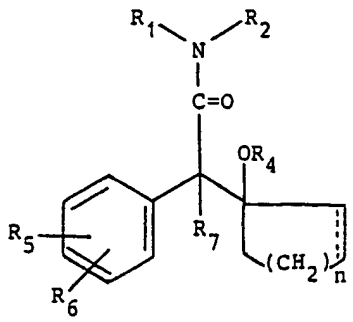
(where R_5, R_6 and R_7 are as defined above) with a cycloalkanone having the formula



(K)

(where n is as defined above) and, if R_4 is C_1—C_6 alkyl, introducing the alkyl group by alkylation.

13. A process for the preparation of a compound having the formula



(X)

in which the dotted line represents optional unsaturation,

R_1 is hydrogen or alkyl of 1 to 6 carbon atoms;

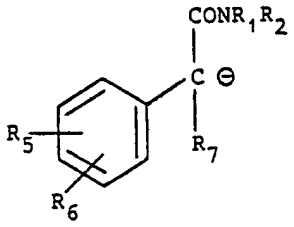
R_2 is alkyl of 1 to 6 carbon atoms;

R_4 is hydrogen or alkyl of 1 to 6 carbon atoms;

R_5 and R_6 are, independently, hydrogen, hydroxyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, aralkoxy of 7 to 9 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, alkylmercapto of 1 to 6 carbon atoms, N-protected amino, halo, trifluoromethyl, or when taken together, methylenedioxy, subject to the proviso that R_5 and R_6 are not both hydrogen;

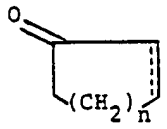
R_7 is hydrogen or alkyl of 1 to 6 carbon atoms; and n is 0, 1, 2, 3 or 4; which comprises

(a) reacting an anion having the formula L



(L)

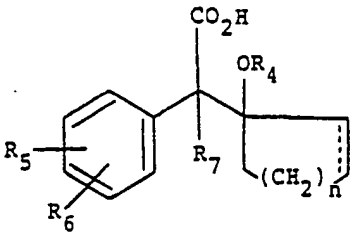
(where R_1, R_2, R_5, R_6 and R_7 are as defined above) with a cycloalkanone or cycloalkenone having the formula M



(M)

(where n and the dotted line are as explained above) and, if R_4 is C_1—C_4 alkyl, introducing the alkyl group by alkylation; or

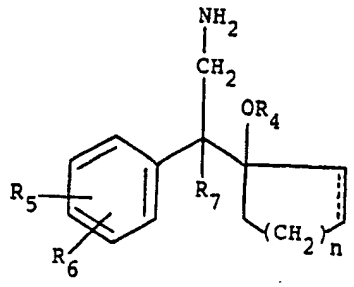
(b) reacting an amine having the formula HNR_1R_2 (where R_1 and R_2 are as defined above) with the acid halide derivative, active ester or anhydride of an acid having the formula N



(N)

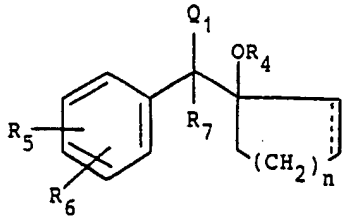
(where R_4, R_5, R_6, R_7, n and the dotted line are as defined above).

14. A process for the preparation of a compound having the formula VI



(VI)

or a pharmaceutically acceptable salt thereof wherein the dotted line, R_4, R_5, R_6, R_7 and n are as defined in Claim 13, which comprises reduction of a compound having the formula P

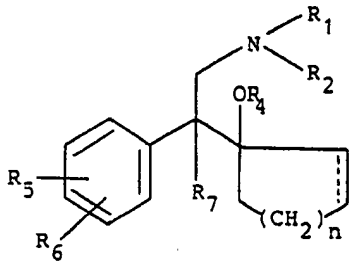


(P)

[where R_4, R_5, R_6, R_7, the dotted line and n are as defined in Claim 13 and Q_1 is selected from —CN; $—CH_2—NO_2$; $—CONH_2$ and —CH = N(OH) and, if Q_1 is —CN, then R_5 and R_6 are as defined in Claim 12].

Patentansprüche für die Vertragsstaaten: BE CH DE FR IT LI LU NL SE

1. Eine Verbindung der Formel



(I)

worin die strichlierte Linie eine gegebenenfalls vorhandene Doppelbindung anzeigt;
R_1 Wasserstoff oder Alkyl mit 1 bis 6 C-Atomen ist;
R_2 Alkyl mit 1 bis 6 C-Atomen bedeutet;
R_4 Wasserstoff, Alkyl mit 1 bis 6 C-Atomen, Formyl oder Alkanoyl mit 2 bis 7 C-Atomen darstellt;
R_5 und R_6 unabhängig voneinander Wasserstoff, Hydroxyl, Alkyl mit 1 bis 6 C-Atomen, Alkoxy mit 1 bis 6 C-Atomen, Alkanoyloxy mit 2 bis 7 C-Atomen, Cyano, Nitro, Alkylmercapto mit 1 bis 6 C-Atomen, Amino, Alkylamino mit 1 bis 6 C-Atomen, Dialkylamino, worin jede Alkylgruppe 1 bis 6 C-Atome aufweist, Alkanamido mit 2 bis 7 C-Atomen, Halogen, Trifluormethyl oder, miteinander genommen, Methylendioxy sind;
R_7 Wasserstoff oder Alkyl mit 1 bis 6 C-Atomen bedeutet; und
n Null, 1, 2, 3 oder 4 ist, oder ein pharmazeutisch annehmbares Salz hievon.

2. Eine Verbindung, wie in Anspruch 1 beansprucht, worin
R_1 Wasserstoff oder Alkyl mit 1 bis 3 C-Atomen bedeutet;
R_2 Alkyl mit 1 bis 3 C-Atomen darstellt;
R_5 Wasserstoff, Hydroxy, Alkoxy mit 1 bis 3 C-Atomen, Chlor, Brom, Trifluormethyl oder Alkyl mit 1 bis 3 C-Atomen ist;

R_6 Alkyl mit 1 bis 3 C-Atomen, Alkoxy mit 1 bis 3 C-Atomen, Chlor, Brom, Trifluormethyl oder Alkanoyloxy mit 2 bis 3 C-Atomen darstellt; und

R_7 Wasserstoff oder Alkyl mit 1 bis 3 C-Atomen bedeutet; oder ein pharmazeutisch annehmbares Salz hievon.

3. Eine Verbindung, wie in Anspruch 2 beansprucht, worin R_5 und R_6 in m- oder p-Stellung sind und n 2 ist.

4. 1-[2-(Dimethylamino)-1-(4-methoxyphenyl)-äthyl]-cyclohexanol oder ein pharmazeutisch annehmbares Salz hievon.

5. Eine Verbindung, wie in Anspruch 4 beansprucht, deren Konfiguration derart ist, daß die spezifische optische Drehung der freien Basenform der Verbindung, gemessen in 95% Äthanol bei etwa 1%iger Konzentration bei 25°C unter Anwendung der Natrium D-Linie, positiv ist.

6. Eine Verbindung, wie in Anspruch 4 beansprucht, deren Konfiguration derart ist, daß die spezifische optische Drehung der freien Basenform der Verbindung, gemessen in 95% Äthanol bei etwa 1%iger Konzentration bei 25°C unter Anwendung der Natrium D-Linie, negativ ist.

7. 1-[2-(Dimethylamino)-1-(3-methoxyphenyl)-äthyl]-cyclohexanol oder ein pharmazeutisch annehmbares Salz hievon.

8. 1-[2-(Dimethylamino)-1-(3-brom-4-methoxyphenyl)-äthyl]-cyclohexanol oder ein pharmazeutisch annehmbares Salz hievon.

9. 1-[2-(Dimethylamino)-1-(4-methoxyphenyl)-äthyl]-cyclohex-2-en-1-ol oder ein pharmazeutisch annehmbares Salz hievon.

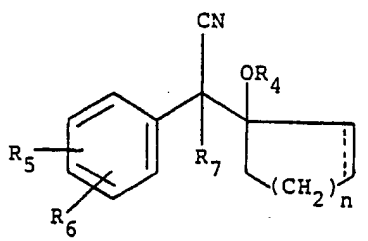
10. Eine Verbindung ausgewählt aus
1-(α-[(Dimethylamino)-methyl]-benzyl)-cyclohexanol,
1-(α-[(Methylamino)-methyl]-benzyl)-cyclohexanol,
1-(α-[(Dimethylamino)-methyl]-benzyl)-cyclohexanolacetat,
1-[1-(4-Chlorphenyl)-2-(dimethylamino)-äthyl]-cyclohexanol,
1-[1-(4-Methoxyphenyl)-2-(methylamino)-äthyl]-cyclohexanol,
1-[1-(4-Bromphenyl)-2-(dimethylamino)-äthyl]-cyclohexanol,
1-[1-(3-Bromphenyl)-2-(dimethylamino)-äthyl]-cyclohexanol,
1-[1-(3-Chlorphenyl)-2-(dimethylamino)-äthyl]-cyclohexanol,
1-[1-(2-Chlorphenyl)-2-(dimethylamino)-äthyl]-cyclohexanol,
1-[1-(3,4-Dichlorphenyl)-2-(dimethylamino)-äthyl]-cyclohexanol,
1-[1-(3,4-Dimethoxyphenyl)-2-(dimethylamino)-äthyl]-cyclohexanol,
1-[2-(Dimethylamino)-1-(4-trifluormethylphenyl)-äthyl]-cyclohexanol,
1-[2-(Dimethylamino)-1-(3-trifluormethylphenyl)-äthyl]-cyclohexanol,
1-[2-(Dimethylamino)-1-(4-methylphenyl)-äthyl]-cyclohexanol,
1-[2-(Dimethylamino)-1-(4-hydroxyphenyl)-äthyl]-cyclohexanol,
1-[2-(Dimethylamino)-1-(3-hydroxyphenyl)-äthyl]-cyclohexanol,
1-[1-(4-Aminophenyl)-2-(dimethylamino)-äthyl]-cyclohexanol,
1-[2-(Dimethylamino)-1-(4-methoxyphenyl)-äthyl]-cyclopentanol,
1-[1-(4-Nitrophenyl)-2-(dimethylamino)-äthyl]-cyclohexanol,
1-[2-(Dimethylamino)-1-(4-methoxyphenyl)-äthyl]-cycloheptanol,
1-[2-(Dimethylamino)-1-(4-methoxyphenyl)-äthyl]-cyclooctanol,
1-[1-(3,4-Dibromphenyl)-2-(dimethylamino)-äthyl]-cyclohexanol,
1-[(2-Dimethylamino)-1-(3-methylphenyl)-äthyl]-cyclohexanol,
1-[1-(4-Bromphenyl)-2-(dimethylamino)-äthyl]-cyclobutanol,
1-[2-(Dimethylamino)-1-(3-methoxyphenyl)-äthyl]-cyclopentanol,
1-[2-(Dimethylamino)-1-(4-methoxyphenyl)-1-methyläthyl]-cyclohexanol und deren pharmazeutisch annehmbare Salze.

11. Pharmazeutische Zusammensetzung umfassend eine Verbindung, wie in einem der Ansprüche 1 bis 10 beansprucht, in Vereinigung mit einem pharmazeutisch annehmbaren Träger.

12. Pharmazeutische Zusammensetzung, wie in Anspruch 11 beansprucht, in Einheitsdosierungsform.

13. Eine Verbindung, wie in einem der Ansprüche 1 bis 10 beansprucht, zur Verwendung als antidepressives Mittel.

14. Eine Verbindung der Formel



(IV)

worin

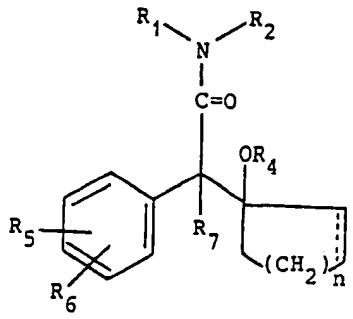
R_4 Wasserstoff oder Alkyl mit 1 bis 6 C-Atomen bedeutet,

R_5 und R_6 o- oder p-Substituenten darstellen und unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, Hydroxyl, Alkyl mit 1 bis 6 C-Atomen, Alkoxy mit 1 bis 6 C-Atomen, Aralkoxy mit 7 bis 9 C-Atomen, Alkanoyloxy mit 2 bis 7 C-Atomen, Alkylmercapto mit 1 bis 6 C-Atomen, Halogen und Trifluormethyl, mit der Maßgabe, daß R_5 und R_6 nicht beide Wasserstoff sind,

R_7 Wasserstoff oder Alkyl mit 1 bis 6 C-Atomen bedeutet und

n Null, 1, 2, 3 oder 4 ist.

15. Eine Verbindung der Formel



(X)

worin die strichlierte Linie eine gegebenenfalls vorhandene Doppelbindung darstellt,

R_1 Wasserstoff oder Alkyl mit 1 bis 6 C-Atomen ist,

R_2 Wasserstoff oder Alkyl mit 1 bis 6 C-Atomen bedeutet,

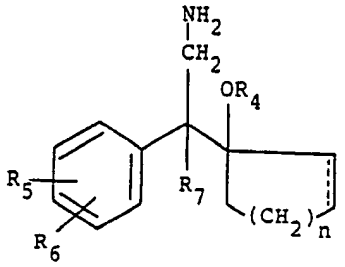
R_4 Wasserstoff oder Alkyl mit 1 bis 6 C-Atomen ist,

R_5 und R_6 unabhängig voneinander Wasserstoff, Hydroxyl, Alkyl mit 1 bis 6 C-Atomen, Alkoxy mit 1 bis 6 C-Atomen, Aralkoxy mit 7 bis 9 C-Atomen, Alkanoyloxy mit 2 bis 7 C-Atomen, Alkylmercapto mit 1 bis 6 C-Atomen, N-geschütztes Amino, Halogen, Trifluormethyl oder, miteinander genommen, Methylendioxy bedeuten, mit der Maßgabe, daß R_5 und R_6 nicht beide Wasserstoff sind,

R_7 Wasserstoff oder Alkyl mit 1 bis 6 C-Atomen darstellt und

n Null, 1, 2, 3 oder 4 ist.

16. Eine Verbindung der Formel

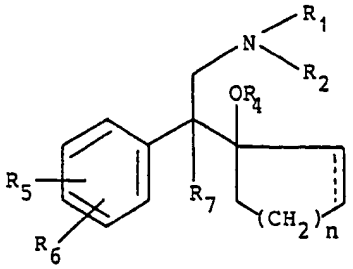


(VIa)

oder ein pharmazeutisch annehmbares Salz hievon, worin die strichlierte Linie, R_4, R_5, R_6, R_7 und n wie in Anspruch 15 definiert sind.

Patentansprüche für den Vertragsstaat: AT

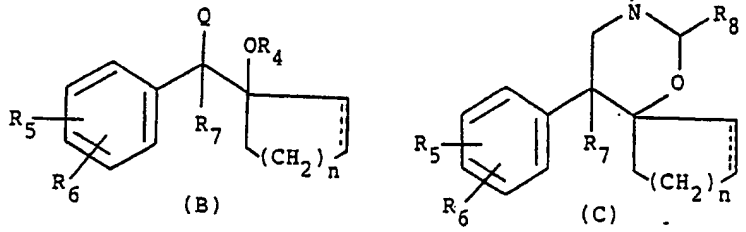
1. Verfahren zur Herstellung einer Verbindung der Formel



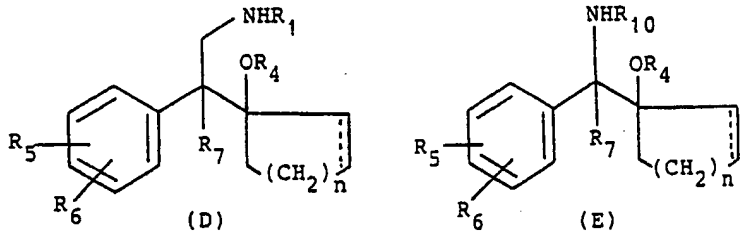
(I)

worin die strichlierte Linie eine gegebenenfalls vorhandene Doppelbindung anzeigt;

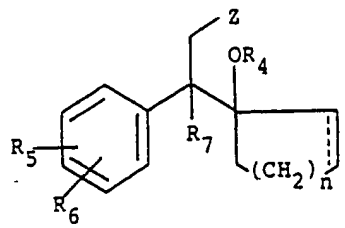
R_1 Wasserstoff oder Alkyl mit 1 bis 6 C-Atomen ist;
R_2 Alkyl mit 1 bis 6 C-Atomen bedeutet;
R_4 Wasserstoff, Alkyl mit 1 bis 6 C-Atomen, Formyl oder Alkanoyl mit 2 bis 7 C-Atomen darstellt;
R_5 und R_6 unabhängig voneinander Wasserstoff, Hydroxyl, Alkyl mit 1 bis 6 C-Atomen, Alkoxy mit 1 bis 6 C-Atomen, Alkanoyloxy mit 2 bis 7 C-Atomen, Cyano, Nitro, Alkylmercapto mit 1 bis 6 C-Atomen, Amino, Alkylamino mit 1 bis 6 C-Atomen, Dialkylamino, worin jede Alkylgruppe 1 bis 6 C-Atome aufweist, Alkanamido mit 2 bis 7 C-Atomen, Halogen, Trifluormethyl oder, miteinander genommen, Methylendioxy sind;
R_7 Wasserstoff oder Alkyl mit 1 bis 6 C-Atomen bedeutet; und
n Null, 1, 2, 3 oder 4 ist, oder eines pharmazeutisch annehmbaren Salzes hievon, welches umfaßt:
(1) Reduktion einer Verbindung einer der Formeln B und C



worin Q $-CONR_1R_2$, $-C=NR_1$, $-CH(OH)NR_2R_2$, $-NR_1-COR_9$, $-N=CY_1Y_2$ oder $-NR_1-CH(OH)-R_8$ bedeutet, R_9 Alkoxy oder C_1—C_5-Alkyl darstellt, Y_1 und Y_2 jeweils ausgewählt sind aus Wasserstoff und Alkyl, derart, daß die Gruppe $=CY_1Y_2$ 1 bis 6 C-Atome enthält, und R_1, R_2, R_4, R_5, R_6, R_7 und n und die strichlierten Linien wie unter Formel (I) definiert sind, vorausgesetzt, daß weder R_5 noch R_6 Cyano, Nitro oder C_2—C_7-Alkanamido ist; oder
(2)(a) Reaktion einer Verbindung der Formel D oder E



(worin R_{10} ein leicht abspaltbarer Substituent ist und R_1, R_5, R_6, R_7, n und die strichlierte Linie wie unter Formel (I) definiert sind, ausgenommen, daß weder R_5 noch R_6 Cyano, Nitro oder C_2—C_7-Alkanamido ist) mit einem Alkylierungsmittel zum Einführen einer oder zwei C_1—C_6-Alkylgruppen (wenn R_1 die Bedeutung H hat) oder einer solchen Alkylgruppe und, wenn notwendig, Abspalten des genannten Substituenten; oder
(b) Reaktion einer Verbindung der Formel D, wie oben definiert, mit einer Carbonylverbindung der Formel Y_1Y_2CO (worin Y_1 und Y_2 wie oben definiert sind) in Anwesenheit eines Reduktionsmittels; oder
(3)(a) Reaktion einer Verbindung der Formel HNR_1R_2 oder HNR_2R_{10} (worin R_1, R_2 und R_{10} wie oben definiert sind) mit einer Verbindung der Formel F

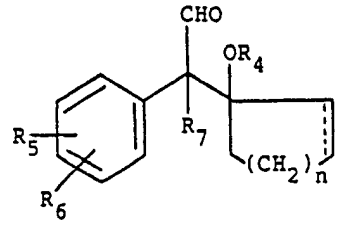


(F)

(worin Z eine abspaltbare Gruppe ist und R_5, R_6, R_7, n und die strichlierte Linie wie unter Formel (I) definiert sind, ausgenommen, daß weder R_5 noch R_6 Cyano, Nitro oder Alkanamido ist) und, wenn notwendig,

Abspalten des Substituenten R_{10}; oder

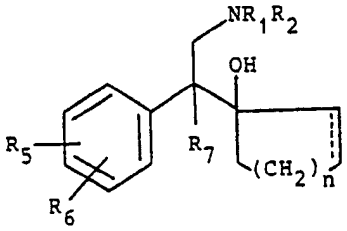
(b) Reaktion einer Verbindung der Formel HNR_1R_2 (worin R_1 und R_2 wie oben definiert sind) mit einem Aldehyd der Formel G



(G)

(worin R_4, R_5, R_6, R_7, die strichlierte Linie und n wie unter Formel (I) definiert sind, ausgenommen, daß weder R_5 noch R_6 Cyano, Nitro oder C_2—C_7-Alkanamido bedeutet) in Anwesenheit eines Reduktionsmittels; oder

(4) Reaktion einer Verbindung der Formel H



(H)

(worin die strichlierte Linie, R_1, R_2, R_5, R_6, R_7 und n wie unter Formel (I) definiert sind) mit einem reaktiven Derivat von Ameisensäure oder einer C_2—C_7-Alkansäure zum Einführen von Formyl oder C_2—C_7-Alkanoyloxy als R_4; oder

(5) Reaktion einer Verbindung der Formel (I), worin R_5 und/oder R_6 Amino ist, durch Mono- oder Dialkylierung oder Acylierung unter Bildung einer Verbindung der Formel (I), worin R_5 und/oder R_6 Mono- oder Di(C_1—C_6-alkyl)amino der C_2—C_7-Alkanamido ist; oder

(6) Diazotieren einer Verbindung der Formel (I), worin R_5 und/oder R_6 Amino bedeutet und Ersetzen des Diazolatsalzes mit einem Nitrit oder Cyanid unter Bildung einer Verbindung, worin R_5 und/oder R_6 Nitro oder Cyano ist; oder

(7) Reaktion einer Verbindung der Formel (I), worin R_5 und/oder R_6 Halogen ist, mit einem Cyanid zum Ersetzen des Halogensubstituenten mit Cyano; oder

(8) Bildung einer Verbindung der Formel (I) oder eines Salzes hievon durch Entfernen einer Schutzgruppe, wobei Amino, N-(C_1—C_6-Alkyl)amino oder Hydroxy als R_5 und/oder R_6 oder Hydroxy als OR_4 erhalten wird; oder

(9) Reaktion einer Verbindung der Formel (I) mit einer Säure zur Bildung eines pharmazeutisch annehmbaren Salzes hievon.

2. Verfahren nach Anspruch 1, worin R_1 Wasserstoff oder Alkyl mit 1 bis 3 C-Atomen bedeutet, R_2 Alkyl mit 1 bis 3 C-Atomen ist, R_5 Wasserstoff, Hydroxy, Alkoxy mit 1 bis 3 C-Atomen, Chlor, Brom, Trifluormethyl oder Alkyl mit 1 bis 3 C-Atomen darstellt, R_6 Alkyl mit 1 bis 3 C-Atomen, Alkoxy mit 1 bis 3 C-Atomen, Chlor, Brom, Trifluormethyl oder Alkanoyloxy mit 2 bis 3 C-Atomen bedeutet und R_7 Wasserstoff oder Alkyl mit 1 bis 3 C-Atomen ist.

3. Verfahren nach Anspruch 2, worin R_5 und R_6 in m- oder p-Stellung sind und n 2 ist.

4. Verfahren nach Anspruch 1, durchgeführt, um 1-[2-(Dimethylamino)-1-(4-methoxyphenyl)-äthyl]-cyclohexanol oder ein pharmazeutisch annehmbares Salz hievon herzustellen.

5. Verfahren nach Anspruch 1, durchgeführt, um 1-[2-(Dimethylamino)-1-(3-methoxyphenyl)-äthyl]-cyclohexanol oder ein pharmazeutisch annehmbares Salz hievon herzustellen.

6. Verfahren nach Anspruch 1, durchgeführt, um 1-[2-(Dimethylamino)-1-(3-brom-4-methoxyphenyl)-äthyl]-cyclohexanol oder ein pharmazeutisch annehmbares Salz hievon herzustellen.

7. Verfahren nach Anspruch 1, durchgeführt, um 1-[2-(Dimethylamino)-1-(4-methoxyphenyl)-äthyl]-cyclohex-2-en-1-ol oder ein pharmazeutisch annehmbares Salz hievon herzustellen.

8. Verfahren nach Anspruch 1, durchgeführt um eine Verbindung ausgewählt aus

1-(α-[(Dimethylamino)-methyl]-benzyl)-cyclohexanol,

1-(α-[(Methylamino)-methyl]-benzyl)-cyclohexanol,

1-(α-[(Dimethylamino)-methyl]-benzyl)-cyclohexanolacetat,

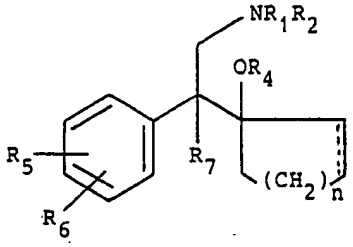
1-[1-(4-Chlorphenyl)-2-(dimethylamino)-äthyl]-cyclohexanol,

1-[1-(4-Methoxyphenyl)-2-(methylamino)-äthyl]-cyclohexanol,

1-[1-(4-Bromphenyl)-2-(dimethylamino)-äthyl]-cyclohexanol,
1-[1-(3-Bromphenyl)-2-(dimethylamino)-äthyl]-cyclohexanol,
1-[1-(3-Chlorphenyl)-2-(dimethylamino)-äthyl]-cyclohexanol,
1-[1-(2-Chlorphenyl)-2-(dimethylamino)-äthyl]-cyclohexanol,
1-[1-(3,4-Dichlorphenyl)-2-(dimethylamino)-äthyl]-cyclohexanol,
1-[1-(3,4-Dimethoxyphenyl)-2-(dimethylamino)-äthyl]-cyclohexanol,
1-[2-(Dimethylamino)-1-(4-trifluormethylphenyl)-äthyl]-cyclohexanol,
1-[2-(Dimethylamino)-1-(3-trifluormethylphenyl)-äthyl]-cyclohexanol,
1-[2-(Dimethylamino)-1-(4-methylphenyl)-äthyl]-cyclohexanol,
1-[2-(Dimethylamino)-1-(4-hydroxyphenyl)-äthyl]-cyclohexanol,
1-[2-(Dimethylamino)-1-(3-hydroxyphenyl)-äthyl]-cyclohexanol,
1-[1-(4-Aminophenyl)-2-(dimethylamino)-äthyl]-cyclohexanol,
1-[2-(Dimethylamino)-1-(4-methoxyphenyl)-äthyl]-cyclopentanol,
1-[1-(4-Nitrophenyl)-2-(dimethylamino)-äthyl]-cyclohexanol,
1-[2-(Dimethylamino)-1-(4-methoxyphenyl)-äthyl]-cycloheptanol,
1-[2-(Dimethylamino)-1-(4-methoxyphenyl)-äthyl]-cyclooctanol,
1-[1-(3,4-Dibromphenyl)-2-(dimethylamino)-äthyl]-cyclohexanol,
1-[(2-Dimethylamino)-1-(3-methylphenyl)-äthyl]-cyclohexanol,
1-[1-(4-Bromphenyl)-2-(dimethylamino)-äthyl]-cyclobutanol,
1-[2-(Dimethylamino)-1-(3-methoxyphenyl)-äthyl]-cyclopentanol,
1-[2-(Dimethylamino)-1-(4-methoxyphenyl)-1-methyläthyl]-cyclohexanol und deren pharmazeutisch annehmbaren Salzen herzustellen.

9. Verfahren nach einem der Ansprüche 1 bis 8, worin die nach dem Verfahren hergestellte Verbindung zur Verwendung als antidepressives Mittel bestimmt ist.

10. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung mit antidepressiver Wirksamkeit, worin eine Verbindung der Formel (I)

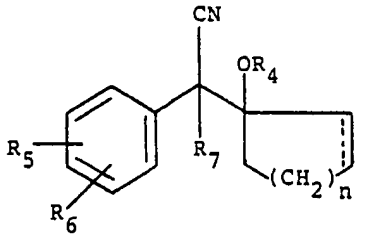


(I)

worin R_1, R_2, R_5, R_6, R_7, n und die strichlierten Linien wie unter Formel (I) in Anspruch 1 definiert sind, oder ein pharmazeutisch annehmbares Salz hievon mit einem pharmazeutisch annehmbaren Träger vereinigt wird.

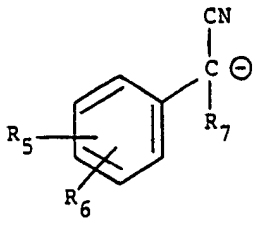
11. Verfahren nach Anspruch 10, worin die Zusammensetzung in Einheitsdosierungsform ist.

12. Verfahren zur Herstellung der Verbindung der Formel



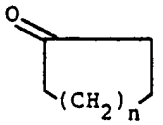
(IV)

worin R_4 Wasserstoff oder Alkyl mit 1 bis 6 C-Atomen bedeutet, R_5 und R_6 o- oder p-Substituenten darstellen und unabhängig ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, Hydroxyl, Alkyl mit 1 bis 6 C-Atomen, Alkoxy mit 1 bis 6 C-Atomen, Aralkoxy mit 7 bis 9 C-Atomen, Alkanoyloxy mit 2 bis 7 C-Atomen, Alkylmercapto mit 1 bis 6 C-Atomen, Halogen und Trifluormethyl, mit der Maßgabe, daß R_5 und R_6 nicht beide Wasserstoff sind, R_7 Wasserstoff oder Alkyl mit 1 bis 6 C-Atomen bedeutet und n Null, 1, 2, 3 oder 4 ist, welches die Umsetzung eines Anions der Formel J



(J)

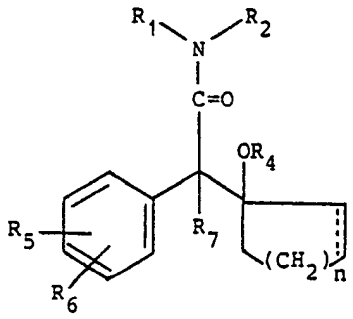
(worin R_5, R_6 und R_7 wie oben definiert sind) mit einem Cycloalkanol der Formel



(K)

(worin n wie oben definiert ist) und, wenn R_4 C_1—C_6-Alkyl bedeutet, Einführen der Alkylgruppe durch Alkylierung umfaßt.

13. Verfahren zur Herstellung einer Verbindung der Formel



(X)

worin die strichlierte Linie eine gegebenenfalls vorhandene Doppelbindung darstellt,

R_1 Wasserstoff oder Alkyl mit 1 bis 6 C-Atomen ist,

R_2 Wasserstoff oder Alkyl mit 1 bis 6 C-Atomen bedeutet,

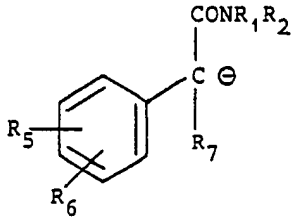
R_4 Wasserstoff oder Alkyl mit 1 bis 6 C-Atomen ist,

R_5 und R_6 unabhängig voneinander Wasserstoff, Hydroxyl, Alkyl mit 1 bis 6 C-Atomen, Alkoxy mit 1 bis 6 C-Atomen, Aralkoxy mit 7 bis 9 C-Atomen, Alkanoyloxy mit 2 bis 7 C-Atomen, Alkylmercapto mit 1 bis 6 C-Atomen, N-geschütztes Amino, Halogen, Trifluormethyl oder, miteinander genommen, Methylendioxy bedeuten, mit der Maßgabe, daß R_5 und R_6 nicht beide Wasserstoff sind,

R_7 Wasserstoff oder Alkyl mit 1 bis 6 C-Atomen darstellt und

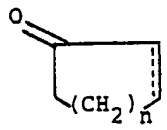
n Null, 1, 2, 3 oder 4 ist, welches umfaßt

(a) das Umsetzen eines Anions der Formel L



(L)

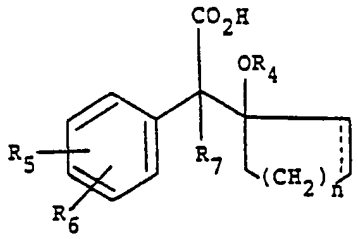
(worin R_1, R_2, R_5, R_6 und R_7 wie oben definiert sind) mit einem Cycloalkanon oder Cycloalkenon der Formel M



(M)

(worin n und die strichlierte Linie wie oben erläutert sind) und, wenn R_4 C_1—C_4-Alkyl ist, Einführen der Alkylgruppe durch Alkylierung, oder

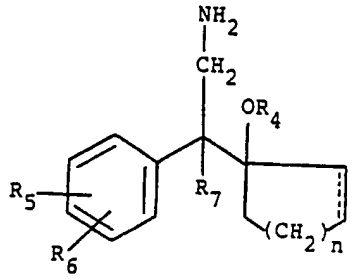
(b) das Umsetzen eines Amins der Formel HNR_1R_2 (worin R_1 und R_2 wie oben definiert sind) mit dem Säurehalogenidderivat, dem aktiven Ester oder dem Anhydrid einer Säure der Formel N



(N)

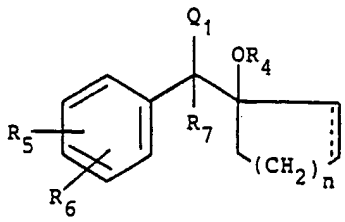
(worin R_4, R_5, R_6, R_7, n und die strichlierte Linie wie oben definiert sind).

14. Verfahren zur Herstellung einer Verbindung der Formel (VI)



(VI)

oder eines pharmazeutisch annehmbaren Salzes hievon, worin die strichlierte Linie, R_4, R_5, R_6, R_7 und n wie in Anspruch 13 definiert sind, welches die Reduktion einer Verbindung der Formel P

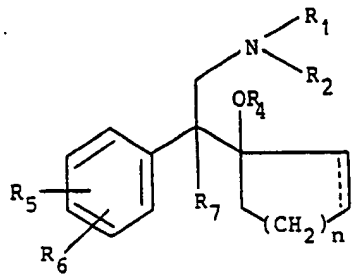


(P)

(worin R_4, R_5, R_6, R_7, die strichlierte Linie und n wie in Anspruch 13 definiert sind und Q_1 ausgewählt ist aus —CN, —CH_2—NO_2, —$CONH_2$ und —CH=N(OH) und, wenn Q_1 die Bedeutung —CN hat, R_5 und R_6 wie in Anspruch 12 definiert sind) umfaßt.

Revendications pour les Etats contractants: BE CH DE FR IT LI LU NL SE

1. Composé de formule



(I)

dans laquelle le segment en traits interrompus représente une non-saturation facultative;

R_1 est l'hydrogène ou un groupe alkyle ayant 1 à 6 atomes de carbone;

R_2 est un groupe alkyle ayant 1 à 6 atomes de carbone;

R_4 est l'hydrogène, un groupe alkyle de 1 à 6 atomes de carbone, formyle ou alcanoyle de 2 à 7 atomes de carbone;

R_5 et R_6 représentent indépendamment l'hydrogène, un groupe hydroxyle, alkyle de 1 à 6 atomes de carbone, alkoxy de 1 à 6 atomes de carbone, alcanoyloxy de 2 à 7 atomes de carbone, cyano, nitro, alkylmercapto de 1 à 6 atomes de carbone, amino, alkylamino de 1 à 6 atomes de carbone, dialkylamino dont chaque groupe alkyle comprend 1 à 6 atomes de carbone, alcanamido de 2 à 7 atomes de carbone, halogéno, trifluorométhyle, ou forment conjointement un groupe méthylènedioxy;

R_7 est l'hydrogène ou un groupe alkyle de 1 à 6 atomes de carbone; et

n a la valeur 0, 1, 2, 3 ou 4; ou un sel pharmaceutiquement acceptable de ce composé.

2. Composé suivant la revendication 1, dans lequel

R_1 est l'hydrogène ou un groupe alkyle de 1 à 3 atomes de carbone;

R_2 est un groupe alkyle de 1 à 3 atomes de carbone;

R_5 est l'hydrogène, un groupe hydroxy, alkoxy de 1 à 3 atomes de carbone, chloro, bromo, trifluorométhyle ou alkyle de 1 à 3 atomes de carbone;

R_6 est un groupe alkyle de 1 à 3 atomes de carbone, alkoxy de 1 à 3 atomes de carbone, chloro, bromo, trifluorométhyle ou alcanoyloxy de 2 ou 3 atomes de carbone;

R_7 est l'hydrogène ou un groupe alkyle de 1 à 3 atomes de carbone; ou un sel pharmaceutiquement acceptable de ce composé.

3. Composé suivant la revendication 2, dans lequel R_5 et R_6 sont en positions méta ou para et n a la valeur 2.

4. Le 1-[2-(diméthylamino)-1-(4-méthoxyphényl)éthyl]cyclohexanol ou un sel pharmaceutiquement acceptable de ce composé.

5. Composé suivant la revendication 4, dont la configuration est telle que la rotation optique spécifique de la forme base libre du composé telle que mesurée dans l'éthanol à 95% à une concentration d'environ 1% à 25°C en utilisant le raie D du sodium, soit positive.

6. Composé suivant la revendication 4, dont la configuration est telle que la rotation optique spécifique de la forme base libre du composé telle que mesurée dans l'éthanol à 95% à une concentration d'environ 1% à 25°C en utilisant la raie D du sodium, soit négative.

7. Le 1-[2-(diméthylamino)-1-(3-méthoxyphényl)éthyl]cyclohexanol ou un sel pharmaceutiquement acceptable de ce composé.

8. Le 1-[2-(diméthylamino)-1-(3-bromo-4-méthoxyphényl)éthyl]cyclohexanol ou un sel pharmaceutiquement acceptable de ce composé.

9. Le 1-[2-(diméthylamino)-1-(4-méthoxyphényl)éthyl]cyclohex-2-ène-1-ol ou un sel pharmaceutiquement acceptable de ce composé.

10. Compose choisi entre:

le 1-(α-[(diméthylamino)méthyl]benzyl)cyclohexanol;

le 1-(α-[(méthylamino)méthyl]benzyl)cyclohexanol;

l'acétate de 1-(α-(diméthylamino)méthyl]benzyl)cyclohexanol;

le 1-[1-(4-chlorophényl)-2-(diméthylamino)éthyl]cyclohexanol;

le 1-[1-(4-méthoxyphényl)-2-(méthylamino)éthyl]cyclohexanol;

le 1-[1-(4-bromophényl)-2-(diméthylamino)éthyl]cyclohexanol;

le 1-[1-(3-bromophényl)-2-(diméthylamino)éthyl]cyclohexanol;

le 1-[1-(3-chlorophényl)-2-(diméthylamino)éthyl]cyclohexanol;

le 1-[1-(2-chlorophényl)-2-(diméthylamino)éthyl]cyclohexanol;

le 1-[1-(3,4-dichlorophényl)-2-(diméthylamino)éthyl]cyclohexanol;

le 1-[1-(3,4-diméthoxyphényl)-2-(diméthylamino)éthyl]cyclohexanol;

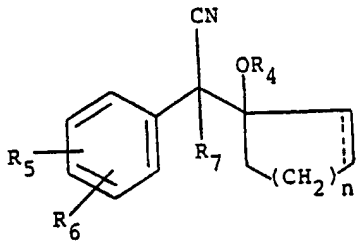
le 1-[2-(diméthylamino)-1-(4-trifluorométhylphényl)éthyl]cyclohexanol;
le 1-[2-(diméthylamino)-1-(3-trifluorométhylphényl)éthyl]cyclohexanol;
le 1-[2-(diméthylamino)-1-(4-méthylphényl)éthyl]cyclohexanol;
le 1-[2-(diméthylamino)-1-(4-hydroxyphényl)éthyl]cyclohexanol;
le 1-[2-(diméthylamino)-1-(3-hydroxyphényl)éthyl]cyclohexanol;
le 1-[1-(4-aminophényl)-2-(diméthylamino)éthyl]cyclohexanol;
le 1-[2-(diméthylamino)-1-(4-méthoxyphényl)éthyl]cyclopentanol;
le 1-[1-(4-nitrophényl)-2-(diméthylamino)éthyl]cyclohexanol;
le 1-[2-(diméthylamino)-1-(4-méthoxyphényl)éthyl]cycloheptanol;
le 1-[2-(diméthylamino)-1-(4-méthoxyphényl)éthyl]cyclooctanol;
le 1-[1-(3,4-dibromophényl)-2-(diméthylamino)éthyl]cyclohexanol;
le 1-[(2-diméthylamino)-1-(3-méthylphényl)éthyl]cyclohexanol;
le 1-[1-(4-bromophényl)-2-(diméthylamino)éthyl]cyclobutanol;
le 1-[2-(diméthylamino)-1-(3-méthoxyphényl)éthyl]cyclopentanol;
le 1-[2-(diméthylamino)-1-(4-méthoxyphényl)-1-méthyléthyl]cyclohexanol et leurs sels pharmaceutiquement acceptables.

11. Composition pharmaceutique comprenant un composé suivant l'une quelconque des revendications 1 à 10 en association avec un support pharmaceutiquement acceptable.

12. Composition pharmaceutique suivant la revendication 11, sous une forme dosée unitaire.

13. Composé suivant l'une quelconque des revendications 1 à 10, destiné à être utilisé comme agent anti-dépresseur.

14. Composé de formule



(IV)

dans laquelle

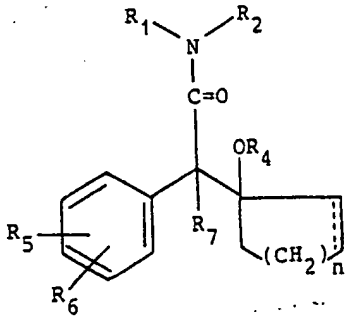
R_4 est l'hydrogène ou un groupe alkyle de 1 à 6 atomes de carbone,

R_5 et R_6 sont des substituants en ortho ou para, indépendamment choisis dans le groupe comprenant l'hydrogène, un radical hydroxyle, alkyle de 1 à 6 atomes de carbone, alkoxy de 1 à 6 atomes de carbone, aralkoxy de 7 à 9 atomes de carbone, alcanoyloxy de 2 à 7 atomes de carbone, alkylmercapto de 1 à 6 atomes de carbone, halogéno et trifluorométhyle, sous réserve que R_5 et R_6 ne soient pas tous deux de l'hydrogène;

R_7 est l'hydrogène ou un groupe alkyle de 1 à 6 atomes de carbone; et

n a la valeur 0, 1, 2, 3 ou 4.

15. Composé de formule



(X)

dans laquelle le segment en traits interrompus représente une non-saturation facultative,

R_1 est l'hydrogène ou un groupe alkyle de 1 à 6 atomes de carbone;

R_2 est l'hydrogène ou un groupe alkyle de 1 à 6 atomes de carbone;

R_4 est l'hydrogène ou un groupe alkyle de 1 à 6 atomes de carbone;

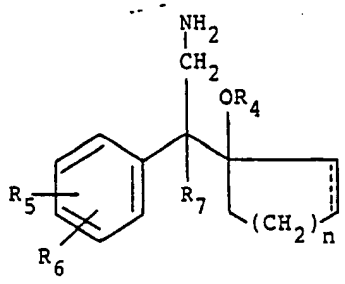
R_5 et R_6 représentent, indépendamment l'hydrogène, un groupe hydroxyle, alkyle de 1 à 6 atomes de carbone, alkoxy de 1 à 6 atomes de carbone, aralkoxy de 7 à 9 atomes de carbone, alcanoyloxy de 2 à 7

atomes de carbone, alkylmercapto de 1 à 6 atomes de carbone, amino protégé sur l'azote, halogéno, trifluorométhyle ou forment conjointement un groupe méthylènedioxy, sous réserve que R_5 et R_6 ne soient pas tous deux de l'hydrogène;

R_7 est l'hydrogène ou un groupe alkyle de 1 à 6 atomes de carbone; et

n a la valeur 0, 1, 2, 3 ou 4.

16. Composé de formule

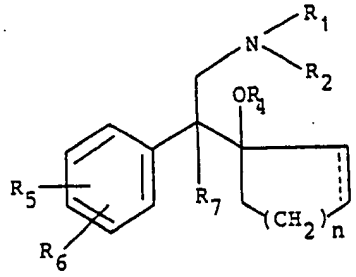


(VIa)

ou un sel pharmaceutiquement acceptable de ce composé, formule dans laquelle le segment en traits interrompus, R_4, R_5, R_6, R_7 et n sont tels que définis dans la revendication 15.

Revendications pour l'Etat contractant: AT

1. Procédé de préparation d'un composé de formule:



(I)

dans laquelle le segment en traits interrompus représente une non-saturation facultative;

R_1 est l'hydrogène ou un groupe alkyle ayant 1 à 6 atomes de carbone;

R_2 est un groupe alkyle ayant 1 à 6 atomes de carbone;

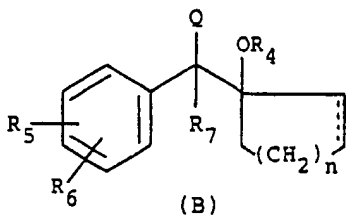
R_4 est l'hydrogène, un groupe alkyle de 1 à 6 atomes de carbone, formyle ou alcanoyle de 2 à 7 atomes de carbone;

R_5 et R_6 représentent indépendamment l'hydrogène, un groupe hydroxyle, alkyle de 1 à 6 atomes de carbone, alkoxy de 1 à 6 atomes de carbone, alcanoyloxy de 2 à 7 atomes de carbone, cyano, nitro, alkylmercapto de 1 à 6 atomes de carbone, amino, alkylamino de 1 à 6 atomes de carbone, dialkylamino dont chaque groupe alkyle comprend 1 à 6 atomes de carbone, alcanamido de 2 à 7 atomes de carbone, halogéno, trifluorométhyle, ou forment conjointement un groupe méthylènedioxy;

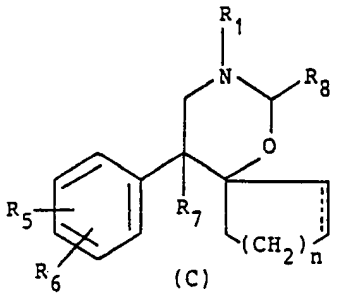
R_7 est l'hydrogène ou un groupe alkyle de 1 à 6 atomes de carbone; et

n a la valeur 0, 1, 2, 3 ou 4; ou d'un sel pharmaceutiquement acceptable de ce composé; qui comprend

(1) la réduction d'un composé répondant à l'une des formules B et C



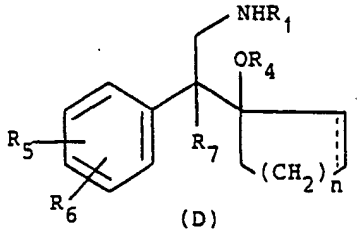
(B)



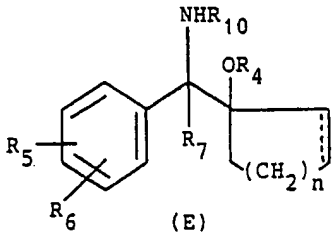
(C)

dans lesquelles Q est un groupe —$CONR_1R_2$; —$C{=}NR_1$; —$CH(OH)NR_1R_2$; —NR_1—COR_9; —$N{=}CY_1Y_2$ ou —NR_1—$CH(OH)$—R_8; R_9 est un groupe alkoxy ou alkyle en C_1 à C_5, Y_1 et Y_2 sont choisis chacun entre l'hydrogène et des groupes alkyle tels que le groupe $=CY_1Y_2$ contienne 1 à 6 atomes de carbone; et R_1, R_2, R_4, R_5, R_6, R_7 et n et les segments en traits interrompus sont tels que définis à propos de la formule I, excepté que ni l'un ni l'autre de R_5 et R_6 ne représente un groupe cyano, nitro ou alcanamido en C_2 à C_7; ou bien

(2)(a) la réaction d'un composé répondant à la formule D ou E



(D)

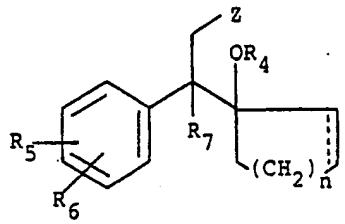


(E)

(dans laquelle R_{10} est un substituant aisément éliminable et R_1, R_5, R_6, R_7, n et le segment en traits interrompus sont tels que définis à propos de la formule I, excepté que ni l'un ni l'autre de R_5 et R_6 ne représente un groupe cyano, nitro ou alcanamido en C_2 à C_7) avec un agent alkylant pour introduire un ou deux groupes alkyle en C_1 à C_6 (si R_1 représente H) ou un tel groupe alkyle et, le cas échéant, élimination dudit substituant; ou bien

(b) la réaction d'un composé répondant à la formule D telle que définie ci-dessus avec un composé carbonylique de formule Y_1Y_2CO [dans laquelle Y_1 et Y_2 sont tels que définis ci-dessus] en présence d'un agent réducteur; ou bien

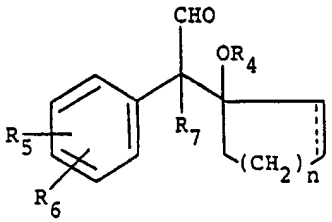
(3)(a) la réaction d'un composé de formule HNR_1R_2 ou HNR_2R_{10} (où R_1, R_2 et R_{10} sont tels que définis ci-dessus) avec un composé répondant à la formule F



(F)

(dans laquelle Z est un groupe partant et R_5, R_6, R_7, n et le segment en traits interrompus sont tels que définis à propos de la formule I excepté que ni l'un ni l'autre de R_5 et R_6 n'est un groupe cyano, nitro ou alcanamido) et, le cas échéant, l'élimination du substituant R_{10}; ou bien

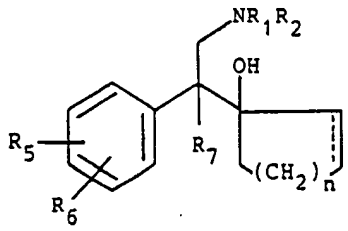
(b) la réaction d'un composé répondant à la formule HNR_1R_2 (dans laquelle R_1 et R_2 sont tels que définis ci-dessus) avec un aldéhyde de formule G



(G)

(dans laquelle R_4, R_5, R_6, R_7, le segment en traits interrompus et n sont tels que définis à propos de la formule I excepté que ni l'un ni l'autre de R_5 et R_6 ne représente un groupe cyano, nitro ou alcanamido en C_2 à C_7) en présence d'un agent réducteur; ou bien

(4) la réaction d'un composé répondant à la formule H



(H)

(dans laquelle le segment en traits interrompus, R_1, R_2, R_5, R_6, R_7 et n sont tels que définis à propos de la formule I) avec un dérivé réactif de l'acide formique ou d'un acide alcanoïque en C_2 à C_7 pour introduire, en tant que R_4, un groupe formyle ou alcanoyloxy en C_2 à C_7; ou bien

(5) la réaction d'un composé répondant à la formule I dans laquelle R_5 et/ou R_6 représentent un groupe amino, par mono- ou dialkylation ou acylation pour former un composé répondant à la formule I dans laquelle R_5 et/ou R_6 représentent un groupe mono- ou di-(alkyle en C_1 à C_6)amino ou alcanamido en C_2 à C_7; ou bien

(6) la diazotation d'un composé répondant à la formule I dans laquelle R_5 et/ou R_6 représentent un groupe amino et le déplacement du sel de diazonium avec un nitrite ou un cyanure pour former un composé dans lequel R_5 et/ou R_6 représentent un groupe nitro ou cyano; ou bien

(7) la réaction d'un composé de formule I dans laquelle R_5 et/ou R_6 représentent un groupe halogéno, avec un cyanure pour déplacer le substituant halogéno avec un substituant cyano; ou bien

(8) la formation d'un composé répondant à la formule I ou d'un sel de ce composé par élimination d'un groupe protecteur pour former un groupe amino, (N-(alkyle en C_1 à C_6)amino ou hydroxy en tant que R_5 et/ou R_6 ou un groupe hydroxy en tant que OR_4; ou bien

(9) la réaction d'un composé répondant à la formule I avec un acide pour former un sel pharmaceutiquement acceptable de ce composé.

2. Procédé suivant la revendication 1, dans lequel

R_1 est l'hydrogène ou un groupe alkyle de 1 à 3 atomes de carbone;

R_2 est un groupe alkyle de 1 à 3 atomes de carbone;

R_5 est l'hydrogène, un groupe hydroxy, alkoxy de 1 à 3 atomes de carbone, chloro, bromo, trifluorométhyle ou alkyle de 1 à 3 atomes de carbone;

R_6 est un groupe alkyle de 1 à 3 atomes de carbone, alkoxy de 1 à 3 atomes de carbone, chloro, bromo, trifluorométhyle ou alcanoyloxy de 2 ou 3 atomes de carbone; et

R_7 est l'hydrogène ou un groupe alkyle de 1 à 3 atomes de carbone.

3. Procédé suivant la revendication 2, dans lequel R_5 et R_6 sont en positions méta ou para et n est égal à 2.

4. Procédé suivant la revendication 1, mis en oeuvre pour la préparation du 1-[2-(diméthylamino)-1-(4-méthoxyphényl)éthyl]cyclohexanol ou d'un sel pharmaceutiquement acceptable de ce composé.

5. Procédé suivant la revendication 1, mis en oeuvre pour la préparation du 1-[2-(diméthylamino)-1-(3-méthoxyphényl)éthyl]cyclohexanol ou d'un sel pharmaceutiquement acceptable de ce composé.

6. Procédé suivant la revendication 1, mis en oeuvre pour la préparation du 1-[2-(diméthylamino)-1-(3-bromo-4-méthoxyphényl)éthyl]cyclohexanol ou d'un sel pharmaceutiquement acceptable de ce composé.

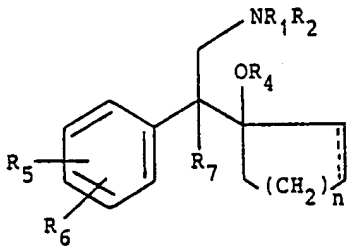
7. Procédé suivant la revendication 1, mis en oeuvre pour la préparation du 1-[2-(diméthylamino)-1-(4-méthoxyphényl)éthyl]cyclohex-2-ène-1-ol ou d'un sel pharmaceutiquement acceptable de ce composé.

8. Procédé suivant la revendication 1, mis en oeuvre pour la préparation d'un composé choisi entre:
le 1-(α-[(diméthylamino)méthyl]benzyl)cyclohexanol;
le 1-(α-[(méthylamino)méthyl]benzyl)cyclohexanol;
l'acétate de 1-(α-[(diméthylamino)méthyl]benzyl)cyclohexanol;
le 1-[1-(4-chlorophényl)-2-(diméthylamino)éthyl]cyclohexanol;
le 1-[1-(4-méthoxyphényl)-2-(méthylamino)éthyl]cyclohexanol;
le 1-[1-(4-bromophényl)-2-(diméthylamino)éthyl]cyclohexanol;
le 1-[1-(3-bromophényl)-2-(diméthylamino)éthyl]cyclohexanol;
le 1-[1-(3-chlorophényl)-2-(diméthylamino)éthyl]cyclohexanol;
le 1-[1-(2-chlorophényl)-2-(diméthylamino)éthyl]cyclohexanol;
le 1-[1-(3,4-dichlorophényl)-2-(diméthylamino)éthyl]cyclohexanol;
le 1-[1-(3,4-diméthoxyphényl)-2-(diméthylamino)éthyl]cyclohexanol;
le 1-[2-(diméthylamino)-1-(4-trifluorométhylphényl)éthyl]cyclohexanol;
le 1-[2-(diméthylamino)-1-(3-trifluorométhylphényl)éthyl]cyclohexanol;
le 1-[2-(diméthylamino)-1-(4-méthylphényl)éthyl]cyclohexanol;
le 1-[2-(diméthylamino)-1-(4-hydroxyphényl)éthyl]cyclohexanol;
le 1-[2-(diméthylamino)-1-(3-hydroxyphényl)éthyl]cyclohexanol;
le 1-[1-(4-aminophényl)-2-(diméthylamino)éthyl]cyclohexanol;
le 1-[2-(diméthylamino)-1-(4-méthoxyphényl)éthyl]cyclopentanol;
le 1-[1-(4-nitrophényl)-2-(diméthylamino)éthyl]cyclohexanol;

le 1-[2-(diméthylamino)-1-(4-méthoxyphényl)éthyl]cycloheptanol;
le 1-[2-(diméthylamino)-1-(4-méthoxyphényl)éthyl]cyclooctanol;
le 1-[1-(3,4-dibromophényl)-2-(diméthylamino)éthyl]cyclohexanol;
le 1-[(2-diméthylamino)-1-(3-méthylphényl)éthyl]cyclohexanol;
le 1-[1-(4-bromophényl)-2-(diméthylamino)éthyl]cyclobutanol;
le 1-[2-(diméthylamino)-1-(3-méthoxyphényl)éthyl]cyclopentanol;
le 1-[2-(diméthylamino)-1-(4-méthoxyphényl)-1-méthyléthyl]cyclohexanol, et leurs sels pharmaceutiquement acceptables.

9. Procédé suivant l'une quelconque des revendications 1 à 8, dans lequel le composé préparé est destiné à être utilisé comme agent anti-dépresseur.

10. Procédé de préparation d'une composition pharmaceutique douée d'activité anti-dépressive, dans lequel un composé répondant à la formule I

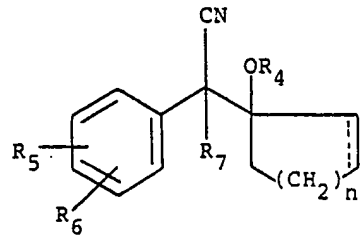


(I)

dans laquelle R_1, R_2, R_5, R_6, R_7, n et les segments en traits interrompus sont tels que définis à propos de la formule I dans la revendication 1, ou un sel pharmaceutiquement acceptable de ce composé, est mis en association avec un support pharmaceutiquement acceptable.

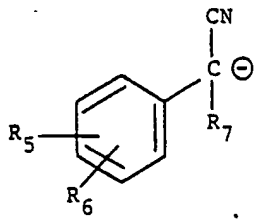
11. Procédé suivant la revendication 10, dans lequel la composition est sous une forme dosée unitaire.

12. Procédé de préparation d'un composé répondant à la formule



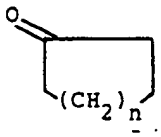
(IV)

dans laquelle R_4 est l'hydrogène ou un groupe alkyle de 1 à 6 atomes de carbone; R_5 et R_6 sont des substituants en ortho ou para, indépendamment choisis dans le groupe comprenant l'hydrogène, un radical hydroxyle, alkyle de 1 à 6 atomes de carbone, alkoxy de 1 à 6 atomes de carbone, aralkoxy de 7 à 9 atomes de carbone, alcanoyloxy de 2 à 7 atomes de carbone, alkylmercapto de 1 à 6 atomes de carbone, halogéno et trifluorométhyle, sous réserve que R_5 et R_6 ne soient pas tous deux de l'hydrogène; R_7 est l'hydrogène ou un groupe alkyle de 1 à 6 atomes de carbone; et n a la valeur 0, 1, 2, 3 ou 4; qui comprend la réaction d'un anion répondant à la formule J



(J)

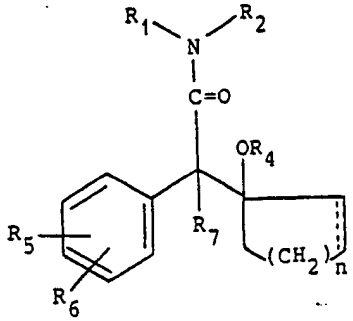
(dans laquelle R_5, R_6 et R_7 sont tels que définis ci-dessus) avec une cycloalcanone répondant à la formule



(K)

(dans laquelle n a la définition donnée ci-dessus) et, si R_4 est un groupe alkyle en C_1 à C_6, l'introduction du groupe alkyle par alkylation.

13. Procédé de préparation d'un composé répondant à la formule



(X)

dans laquelle le segment en traits interrompus représente une non-saturation facultative.

R_1 est l'hydrogène ou un groupe alkyle de 1 à 6 atomes de carbone;

R_2 est un groupe alkyle de 1 à 6 atomes de carbone;

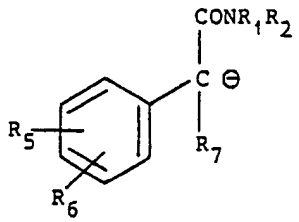
R_4 est l'hydrogène ou un groupe alkyle de 1 à 6 atomes de carbone;

R_5 et R_6 représentent indépendamment l'hydrogène, un groupe hydroxyle, alkyle de 1 à 6 atomes de carbone, alkoxy de 1 à 6 atomes de carbone, aralkoxy de 7 à 9 atomes de carbone, alcanoyloxy de 2 à 7 atomes de carbone, alkylmercapto de 1 à 6 atomes de carbone, amino protégé sur l'atome d'azote, halogéno, trifluorométhyle ou bien R_5 et R_6 forment conjointement un groupe méthylènedioxy sous réserve que R_5 et R_6 ne soient pas tous deux de l'hydrogène;

R_7 est l'hydrogène ou un groupe alkyle ayant 1 à 6 atomes de carbone; et

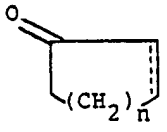
n a la valeur 0, 1, 2, 3 ou 4; qui comprend

(a) la réaction d'un anion de formule L



(L)

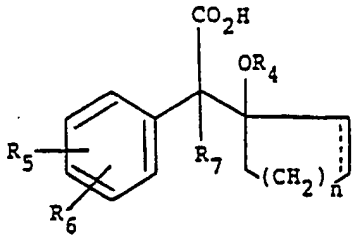
(dans laquelle R_1, R_2, R_5, R_6 et R_7 sont tels que définis ci-dessus) avec une cycloalcanone ou une cycloalcénone répondant à la formule M



(M)

(dans laquelle n et le segment en traits interrompus sont tels qu'indiqués ci-dessus) et si R_4 est un groupe alkyle en C_1 à C_4, l'introduction du groupe alkyle par alkylation; ou bien

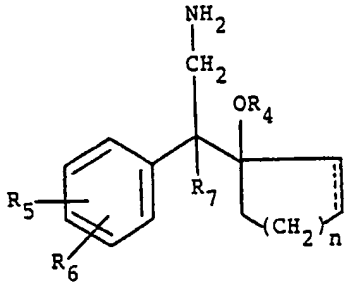
(b) la réaction d'une amine répondant à la formule HNR_1R_2 (dans laquelle R_1 et R_2 sont tels que définis ci-dessus) avec l'halogénure d'acide, l'ester actif ou l'anhydride d'un acide répondant à la formule N



(N)

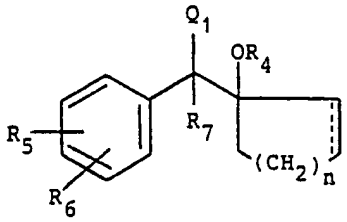
(dans laquelle R_4, R_5, R_6, R_7, n et le segment en traits interrompus sont tels que définis ci-dessus).

14. Procédé de préparation d'un composé de formule VI



(VI)

ou d'un sel pharmaceutiquement acceptable de ce composé, formule dans laquelle le segment en traits interrompus, R_4, R_5, R_6, R_7 et n sont tels que définis dans la revendication 13, procédé qui comprend la réduction d'un composé de formule P



(P)

[dans laquelle R_4, R_5, R_6, R_7, le segment en traits interrompus et n sont tels que définis dans la revendication 13 et Q_1 est choisi entre —CN; $—CH_2—NO_2$; $—CONH_2$ et —CH=N(OH) et, si Q_1 est un groupe —CN, R_5 et R_6 sont alors tels que définis dans la revendication 12].